Proceedings of the

TEACHERS' SEMINAR ON PHARMACOGNOSY

AUGUST 9-13, 1959

HELD UNDER THE AUSPICES OF THE AMERICAN
ASSOCIATION OF COLLEGES OF PHARMACY

AT

College of Pharmacy

University of Illinois

Chicago

Edited by

FRANK A. CRANE

**The Teachers' Seminars Are Made Possible by the Support of
The American Foundation for Pharmaceutical Education**

FOREWORD

One of the most potent projects which resulted from the recommendations of the Pharmaceutical Survey was the establishment of the series of Teachers' Seminars in the various professional subject matter fields which comprise the pharmaceutical curriculum. It was a privilege for the University of Illinois College of Pharmacy to act as host to the eleventh in this series during the week of August 9 to 13, 1959.

The occasion was a culminating event marking the close of the hundredth year since the founding of the Chicago College of Pharmacy, the antecedent college to the present University of Illinois College of Pharmacy. It was further enhanced by the fact that the Plant Science Seminar, founded by Edwin L. Newcomb in 1924 met on the two days preceding the seminar and was attended by many of the same group of scientists. It was at this meeting that the Plant Science Seminar as it was originally organized merged its purposes into a new entity, the American Society of Pharmacognosy which was born by the adoption of a new constitution and by laws on August 10, 1959.

The program for this Seminar was selected from a series of suggestions sent in by members of the section of Teachers of Biological Sciences of the A.A.C.P. The organizing committee is indebted to these suggestions for many of the topics which were presented. It wishes to thank those who submitted the list of suggested topics for their invaluable help.

It expresses thanks to the thirty other faculty members whose excellent papers and presentations made valuable contributions to the teaching of Pharmacognosy.

On behalf of the ladies who accompanied their husbands a word of appreciation goes to the wives of faculty members of the University of Illinois College of Pharmacy for their enjoyable social program and to the Ciba Company for contributing the bus transportation which was so necessary.

The appeal of the program is attested by the attendance of 112 participants from 58 Colleges of Pharmacy in the United States, 2 Colleges of Pharmacy in Canada and one from the Philippine Islands. A total of 142 persons participated in one or more of the scientific and social meetings.

A special word of thanks must be extended to the officers and directors of the American Foundation for Pharmaceutical Education for the financial support without which the Seminars could not be held.

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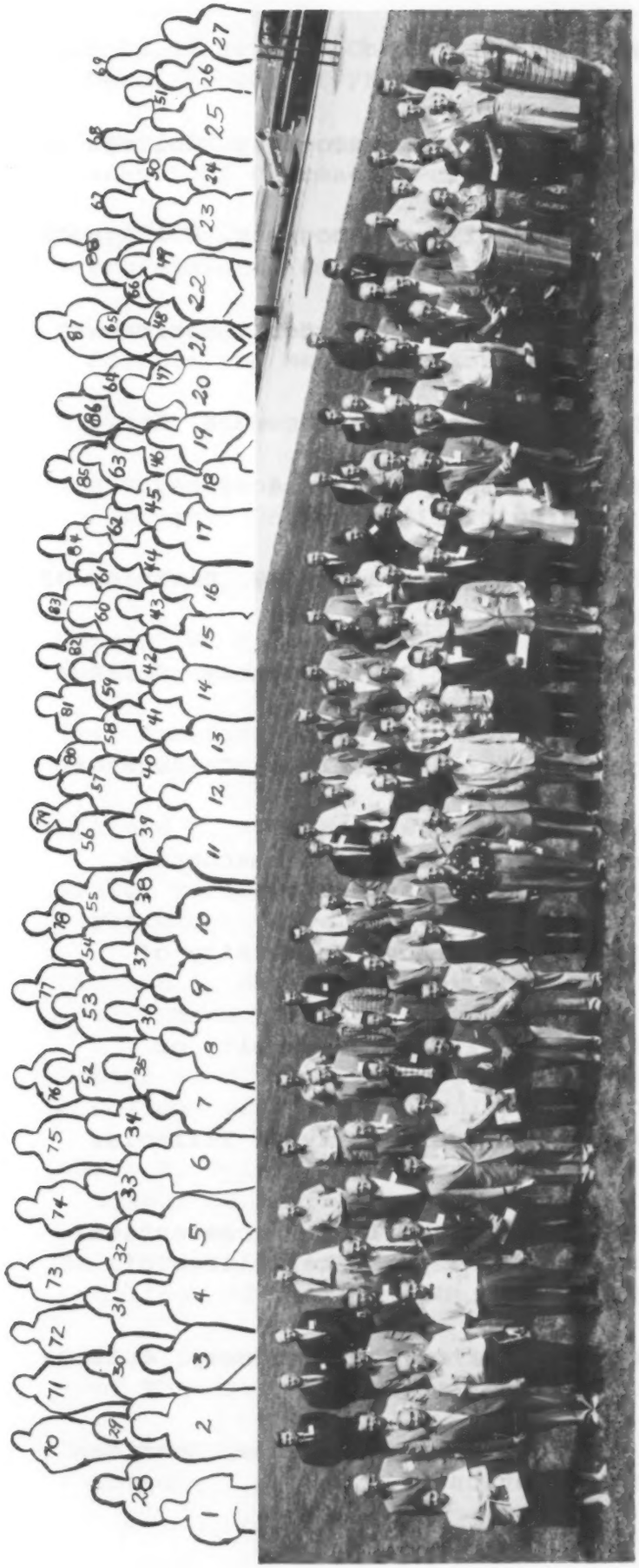

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WELCOME

APPRAISING A COLLEGIATE AND PROFESSIONAL PROGRAM

H. E. Longenecker

It is most important that you should come together to discuss common problems of teaching and the preparation of the oncoming generation of pharmacy students in pharmacognosy. It is no longer enough that educational institutions simply grow by accretion and occasionally by substitution. It is essential that we review periodically the basic elements of the curriculum for the provision of competent and up-to-date programs of instruction.

This generation of youth is going to seek eagerly for a level and kind of instruction that we have not experienced in the past. Witness for a moment what is happening in our high schools today. I'm sure you have read or heard about a report from Dr. Conant dealing with the American High School. This report was but one of many facets in the reexamination of the American High School curriculum. Perhaps, as a result of its impact, some of you have already experienced the problem of accepting and giving recognition to youngsters graduating from our high schools who have requested and have received from your institution credit for advanced standing on the basis of high quality work done in their high schools. This again then represents a pattern of development of the young people who are on their way to you.

During the past summer, I was privileged to see several admittedly small but I think rather significant high school groups, in extensive and intensive programs of collegiate level work. These high school students had just completed the junior year. They were in several colleges which had received assistance from the National Science Foundation to provide opportunities for able youngsters interested in science. Not all of the students who will come to the schools and colleges of pharmacy will be of the intellectual calibre of those selected for the high school science program.

We recognize that our colleges in consequence must deal with a whole series of problems that were so well covered in that magnificent statement of the American Council on Education "They came for the best of reasons". You who teach know many of these reasons. And you know that in dealing with the broad cross section of American youth who have decided to

enter the colleges of Pharmacy, you face a constant and continuing challenge. It is to meet them on their own terms at the start and yet not compromise with standards of excellence and performance that must be demanded if we are to be assured of a satisfactory, competent, respected and honored graduate in a four or five year period.

This is the kind of challenge that I see coming to you with increasing intensity. I think it requires on the part of each of us who has the privilege of some direct connection with young students, the opportunity and the obligation to search our own minds and our own consciences as you are going to do in these next few days in regards to your own curricula.

Your subject has been one about which many have asked questions. Will it be the same as it has been in the past curriculum? What changes are going to be introduced? Are there important techniques that need to be given consideration? Are there some aspects of the subject that can be dropped by the wayside? Are there some that can be better undertaken by others? Are there some that you are not now undertaking that should be added?

I'm sure that these and many other kinds of questions will be renewed in the next few days. As you deal with them I hope that you will always be conscious of the basic objectives of the institution of which your college is a part--the basic objective to provide broadened educational opportunities for the youth of our nation. We sorely need to prepare educated citizens as well as trained specialists. This obligation on the part of the colleges of pharmacy is being accepted more and more as you move into your new five-year curriculum structure. As you deal with the problems of pharmacognosy and some of the other phases of the curriculum on the side, may I again plead with you that you be ever conscious of the relevance of your work to the role of the entire university. These are important issues that must have a first place in your thinking, as they have a first place in curricular planning and educational planning in all American institutions.

Thank you for coming. I hope that your stay will be pleasant on our campus and in Chicago.

GREETINGS

W. Paul Briggs

I am privileged to attend this 10th AACP Teachers' Seminar, and on behalf of the Officers and Directors of the Foundation, to bring you best wishes for a successful meeting.

The Foundation considers these teacher refresher programs one of the most important of its sponsored projects for the advancement of pharmaceutical education. We are happy that AFPE, with funds provided by the drug trade and industry, can provide support for these soundly conceived and productive meetings.

As teachers of pharmacognosy we hope you will continue to participate, and also stimulate your students to submit essays, in competition for the annual E. L. Newcomb Memorial Awards for original work in Dr. Newcomb's field of pharmacognosy.

At the request of the AACP Executive Committee the Board of Grants will hereafter attempt to announce AFPE graduate Fellowships prior to March 31 each year. We are anxious that all current Fellows seeking renewal of their grants and all applicants for new Fellowships be informed that applications must now be submitted between February 15 and March 15 in order to be considered by the Board for awards starting the following September. In the past applications were received up to April 15. You can help us, and the students at your colleges, if you will insure that this change in filing date is known to all concerned.

I commend your Chairman, Dr. George L. Webster and his committee associates, Drs. Frank A. Crane, Varro E. Tyler, Jr., Ralph F. Voigt, and Heber W. Youngken, Jr., for developing an especially interesting and broadly based seminar program for 1959. I am sure all seminarians will profit from attendance and, in turn, will extend their personal benefits to their colleagues and students.

THE IMPLEMENTATION OF SEMINAR SUGGESTIONS

Louis C. Zopf

This, the eleventh annual seminar of pharmacy teachers, is again co-sponsored by the American Association of Colleges of Pharmacy and the American Foundation for Pharmaceutical Education. It is perhaps in order for us to review the stated purpose for which these seminars were developed. I quote from the pharmaceutical survey: "The primary purpose of these seminars is that of providing needed opportunity for the members of the teaching staffs and for graduate students to come into fruitful contact and to keep pace with progressive content and methods of pharmaceutical teaching." Many of us have participated in each of these seminars, sharing ideas and experiences, and presenting our problems for evaluation and possible solution. The keynote of the seminars has been the dissemination of the "how" and "why" of our syllabi, stressing particularly the needs for improved teaching methods coupled with the use of modernized facilities and teaching aids.

The value of these seminars is evident when one visits our Colleges of Pharmacy. Improved Teaching, revitalized and modernized syllabi, and the adaptation of the new five-year program are illustrative of seminar stimuli. It is common to hear comments such as: "At our seminar last year we discussed thus and so. -- As a result I have modified my lecture notes and changed my laboratory procedure." If any teacher fails to gain constructively from this or any of the past seminars, then that individual lacks one of the very basic requisites of a good teacher, namely an open mind.

It is encouraging to observe, as the various specialists meet, that one always finds a favorable percentage of new, young teachers who - while they seek to learn from experienced minds - also present a challenge and a warning to the oldsters that new methodology modifies the manner and subject matter of standard courses. Here the young teacher presents his ideas and concepts to the master tutor; here both should discuss and evaluate methods of transmitting ideas to students - a group best defined as individuals who pay to learn but who rebel and oppose becoming educated.

Teaching is a form of selling. It is a difficult but rewarding experience to sell education as an investment. Timidity in the sales talk cannot be tolerated, but sincerity

and enthusiasm are fundamental. The value of the commodity varies from individual to individual, but basically it is dependent upon his careful selection and acquisition of basic facts and information.

In the early stages of educational reform, much attention was given to what is now known as general education. The pioneers in education adopted the "elective" principle which opened the curriculum to new knowledge and which contributed strategically to changing the college professor from a drill master to a teacher. The recitation system and rote memory program gave way to lecture, laboratory, and seminar methods. Now emphasis is placed upon the capacity of the student's mind, and he is evaluated on the basis of his intellectual achievement.

Education as a commodity is minutely subdivided into specialties, professions, vocations, and avocations. In our work we are constantly confronted with the competitive selling power of other teaching personalities, their methods of presentation, as well as the immediate recognition of the practical application of course material. A commodity cannot be sold by one who lacks interest, because nothing reflects so garishly as insincerity and incompetency relative to subject matter.

This week we share ideas for the teaching of pharmacognosy, the subject -- dare I say -- which twelve years ago was considered a declining discipline and which was frequently classified by the uninformed as antiquated and unnecessary in the undergraduate program. Pharmacognosy suffered because of the retention of a teaching principle stressing rote memorization and the declining use of vegetable drugs <u>per se</u>. The acceptance of the expanded and fundamentally different approach to the teaching of pharmacognosy met with internal hostility. The transition from a totally morphological and/or combined chemical and pharmacological consideration of vegetable material did much to secure and re-establish pharmacognosy as a modern discipline. Much of the courage for change developed as a result of the uninhibited discussion which occurred at these seminars and at the plant science seminars, another striking example of the value of such meetings. Here we convene groups of specialists who meet in security and isolation from the pressures and criticisms of other pharmaceutical disciplines. Informality and fellowship encourage completely analytical and totally critical discussions of subject matter and course organization. This is

the zenith of attributes possessed by our seminars. Each discipline here dares to expose its familial controversies, admit its inadequacies, and re-evaluate the items which constitute the subject. Here, as experts, you meet with men of experience who may be opinionated, but whose tenure and guidance will prevent the young teacher from stumbling where others have fallen. Our initial provincial attitudes must be replaced by a cosmopolitan outlook if pharmacognosy is to be assimilated and properly allocated within the general educational pattern of pharmacy.

Just as a partnership exists between science and industry, there also prevails an interdisciplinary relation between the specialties of pharmaceutical education. Application of principles of chemistry, biology, and pharmacy to pharmacognostic developments are acknowledged and, therefore, the success of your own program is dependent upon the cooperative understanding of these other specialties. The printing press was a wonderful invention. It is the means by which our literature and the history of our own efforts may be preserved for posterity. Literature records in detail the problems, the findings, and the pursuits of many avenues of science. These chronicles expose the "tell-tale gray," the :solenized white," and the "ragged undergarments," as well as the "multi-colored saris." This is said in an effort to encourage you to share your voluminous findings with the other specialists in the pharmaceutical field. Let us not become inhibitory or selfish in our actions. Those of us with graying hair (or absence thereof) might well remember a statement made by Dr. Walter Dill Scott, past-President of Northwestern University, while he was president of the American Council on Education. He said, "There are today in America many individuals who are called leaders in education but whose age of plasticity was passed before the dawn of the mechanical age. Even our most useful educators are unduly strained by the inertia of tradition. There are educational associations whose chief concern is to hold all educational institutions to a traditional standard. In such associations, the mob mind resents any appearance of originality." This statement, made over thirty years ago, is certainly apropos at this time. Those of us with administrative responsibilities and of maturing years must remove ourselves from the academic groove of tradition and assume the obligation of the true teacher and scientist. To paraphrase Matthew Arnold: Remember that the function of the teacher is to teach and to propagate the best that is known and taught in the world; to teach the current knowledge of the subjects we profess - sifting, analyzing, assorting, laying down principles; to propagate, to multiply facts on which to

base principles, experimenting, and testing, the best that is known and taught in the world. -- Nothing less can satisfy a teacher worthy of the name.

The value of our seminars extends beyond the defined general purposes. It invades the arena where teachers believe most things stop -- namely in the office of the Dean. These seminars furnish you, the teachers, with defensive mechanisms and ammunition to support your immediate requests which, in turn, supply your Dean with background information with which to defend his budgetary requests.

Our member colleges are grateful to the American Foundation for Pharmaceutical Edication for financing these seminars, but the Association benefits only as the individual college reflects progress and improvement in its teaching program. It is incumbent upon me to generalize on some of the rather well-known things in order to emphasize the necessity for each group to share in advancement and change. Remember, it is essential that we have a rapport and respect between and for colleagues who have the responsibility of complementing our teaching. It is the total educational program which is reflected by our graduates.

To implement seminar recommendations requires more than merely reading or listening to papers, participating in workshops, etc. It requires enthusiasm, aggressiveness, and cooperation on the part of the teacher. The recommendations will need consideration from the standpoint of their effect and position in the overall educational pattern. They must become an integral part of the matrix. For this kind of attitude, pharmacognosy deserves more than cursory acknowledgement.

Boundary lines for limits of disciplines are difficult to define. The province of each subject has a basic pattern, but all subject content cannot be declared independent ground. There will of necessity be certain repetitive materials appearing in several courses. The use of these materials may be intirely different. The implementation of recommendations from the specific disciplines must be evaluated on the basis of developing a professional person, of designing an individual who is competent and qualified to perform pharmaceutical services within society's orbit.

Every teacher feels that his subject, his method of teaching, and his contribution to the individual are of primary importance. This is another attribute of a good teacher and is a fine attitude provided it is mitigated and flavored with discretion and with a dash of sympathetic understanding for the student. A provincial attitude will adversely affect your own discipline and dwarf the educational pattern as a whole. It forms a weakness in the organism which is reflected in the diminution of the student's competence and success.

The comment of a teacher relative to any subject, but particularly about another course, is accepted with eagerness and authenticity. A careless or slighting remark made in a facetious manner may have repercussions which will be embarrassing. These may be the catalysts that distort the educational process of students. Tartness of tongue and indiscretions of speech have done much damage.

Seminars are costly only if they fail to improve pharmaceutical education. Improvement will be reflected when new ideas of this and other seminars are consolidated and implemented as parts of a total educational pattern. Discretion and cooperation, coupled with objective thinking, will result in an improved program for pharmaceutical education.

OBSERVATIONS ON CURRENT TEACHING IN PHARMACOGNOSY

Melvin W. Green

I feel distinctly honored on being invited to address this important teacher's seminar in the field of pharmacognosy. I am sure that before the week is over you will have been reminded many times of the fact that your field is the one pharmaceutical science (perhaps with the exception of pharmacy proper) which is unique to the entire field of education. Because pharmacognosy is in this unique position, **you** have an opportunity, each of you, to build a Department of Pharmacognosy in your institution to which others, even outside the College of Pharmacy, can point with pride. This subject is so important that I regret that it will not be possible for me to spend as much time attending the seminar as I would like.

My topic deals with observations on current teaching in pharmacognosy and these observations soon boil down to the fact that pharmacognosy is a field beset with problems, in fact, many problems, and in fact **many** problems which are relatively acute. This is not disturbing. In the history of any science, I believe that you will find times when such science needs a new definition, and a fresh outlook and appears, for a time, to have outgrown its usefulness. I am sure you are all familiar with the fact that it was not too many decades ago when young men and women were discouraged from entering the field of physics because it was believed that all the problems of consequence in this important field were solved.

I had a personal experience which I would like to relay to you since it involves this very concept. While I was still a graduate student, I had an opportunity to attend a meeting of the Federated Society of Biological Sciences. As you know, this Society embraces professional organizations of pathologists, physiologists, pharmacologists, and others in the biological field.

Up to that time, I had had very limited contact with advanced scholarship in the area of pharmacology, but since I was originally a pharmacist, this was an important field

to me and at that particular stage of my development I considered pharmacology to be the cornerstone of the teaching of medicine. When I noted from the program of the Federated Societies that the Pharmacology Society was having a luncheon, I decided to attend to see what pharmacologists en masse looked like and to learn something of the problems of graduate and research pharmacology.

I anticipated a typical luncheon to be followed by some eminent scientific speaker in this field or related fields who would give a stimulating talk outlining some of the recent accomplishments in the field and some of the important research problems to come. I was in for a surprise and, I must admit, somewhat of a shock. The luncheon meeting turned out to be little better than a bull session for discussing the unfavorable position of pharmacology in medical schools and what could and should be done about it. A note of pessimism ran through it all as it was indicated that no one outside of the field seemed to know what pharmacology was, no one seemed to care whether pharmacology was taught in the medical schools or not, it was impossible to stimulate young men to go into graduate work in pharmacology, and perhaps the time had now come for pharmacology to be removed from the medical school just as botany once had. At this time, of course, there were still vestiges of the old materia medica approach to pharmacological and therapeutic teaching in the medical schools, but there were a sizable number of men of real stature like Dennis Jackson of Cincinnati, Dr. Edmonds of the University of Michigan, Dr. Sollmann of Western Reserve present. The more scientific pharmacologists were equally depressed and a great deal of the concern seemed to revolve around the fact that the science of pharmacology was not properly defined and that it was difficult to define because of the overshadowing importance of such strong disciplines as the newer chemical pathology, biochemistry, and invigorated bacteriology.

I cite this situation because you all know what has happened to the field of pharmacology in just a few years since this time, a time that was identified with the middle 30's, and it points up the fact that fields, that are recognized as vigorous, strong, fields, have all had these periods of the doldrums.

While I have mentioned and implied that pharmacognosy is somewhat in this position, I would not want to leave the impression with you that it is my opinion that all is dark, for

I recognize that there are several centers of considerable vigor in pharmacognosy and that there is a re-definition of and development of a so-called "newer" Pharmacognosy in process and about which the next speaker will tell you some details. It is this light in the somewhat dim world that leads us to hope that many of these problems can be faced at this meeting, at least, if not solved in whole or in part.

One of the first and foremost problems facing the teaching of Pharmacognosy appears to me to be the problem of re-defining the field in keeping with modern practices in pharmacy and medicine generally. The causes for the need for such a re-definition are many and certainly one of those causes is the rapid rate of obsolescence of drugs which has hit all phases of pharmacy and, parenthetically medicine, but which has hit the dominion of naturally occurring drugs particularly hard with the exception of the newer areas largely springing from mycology. Pharmacognosy is not alone in having this problem, since it has hit the other pharmaceutical sciences very hard, too. The turnover of organic medicinals is so rapid that there is a great temptation for pharmaceutical chemists to resort to mere cataloging. The number of galenical preparations that we have considered to be standard and eternal in pharmacy that are rapidly passing by the wayside is rather frightening to many of us. This is causing people in the other pharmaceutical sciences to do a great deal of re-defining of their situations, also. The point of the matter is that the time is now when we must be willing to be ruthless in casting aside old drug friends where necessary in every field making room for discussions of the newer drugs and principles. We must keep ourselves mindful of the fact that our students will be practicing in the next century.

A second factor necessitating the re-definition of the field of pharmacognosy is the apparent limitation in the need for rigorous training in the qualitative identification of drugs of natural origin. Many of the techniques would appear, at least to an outsider, to offer very little in the way of basic understandings that are essential to the professional life of a pharmacist regardless of the location of his practice. The Crane summary of the excellent questionnaire that was prepared by the local committee for this Teacher's Seminar and which has been circulated, indicates the degree of stress put upon such qualitative testing and I cannot refrain from raising the question of the amount of stress really needed. At a time when almost the entire therapeutic armamentarium of

the physician centered on vegetable drugs, perhaps this was a most important area. In times such as we are facing, it would appear to an outsider that there are many activities that are pharmacognostical in viewpoint which might be more productive in making a pharmacist an expert on drugs. In some institutions, the impression has been gained that almost the sole purpose of Pharmacognosy is this rather limited area of identification.

Another related problem which makes it somewhat difficult to re-define the field, I have termed the problem in invading overlapping fields. When pharmacognosists first sensed the need for such a re-definition, there was a temptation simply to make the pharmacognosy course another course in pharmacology or in pharmaceutical chemistry or in biochemistry. This engendered a certain degree of protest on the part of those whose fields were invaded and made it seem particularly unclear where pharmacognosy should go.

This alleged invasion was not of much concern to some of us, because it is well known that many of our strongest academic fields have come into being by a certain amount of such invasion although I think a better term would be cross utilization of the techniques of related fields.

Biochemistry is a strong field today and yet it represents a hybridization of chemical and biological disciplines which was initially looked upon with no little suspicion. The concern was present, principally, because the resultant hybrid often represented neither good biology nor good chemistry. As time went on and biochemists were better trained in the basic underlying disciplines, and brought this training to the borderline discipline, the resultant product became a strong one, indeed. One finds the same situation in pharmacology where the techniques have all been borrowed from physiology and biochemistry and, in fact, a survey of nearly any issue of either the American Journal of Physiology or the Journal of Biological Chemistry will disclose the fact that a number of the authors are pharmacologists.

Pharmacognosy, during this period of re-definition, I am sure will borrow in the same fashion and as long as they do so out of strength and not out of weakness, the field is sure to become cogent.

To me, one of the high points of the Crane questionnaire is the indication of the number of people teaching pharmacognosy who are not trained specifically in pharmacognosy. Personally I would like to see more of this, particularly the introduction of those people who are trained in the non-pharmaceutical sciences but whose scientific training can bring a fresh point of view to pharmacognosy.

Another problem that relates to the re-defining of the field springs from the comparatively recent addition of fresh material which originally did not belong to the field of pharmacognosy. I am thinking of the teaching of parasiticides, insecticides, vaccines, sera and other related materials. I would not be so presumptious as to say whether it is proper that such extraneous materials should be brought into the pharmacognosy program. However, I would like to point out that most of these materials bear natural familial relationships to other well defined sciences. This is particularly true of the biologicals of the vaccine and serum groups. The important consideration here, in my judgment, is that, if they are to be covered in pharmacognosy, they must be taught in as scholarly a fashion as they would be covered in their natural science setting. This poses an important problem, because the average teacher of Pharmacognosy often is not prepared properly to teach such material but is, in effect, reviewing a textbook with the students.

The last topic that I wish to refer to in this area is the problem of defining research. In the last analysis, I suppose the field of pharmacognosy will be defined by the direction taken by its research. Fifteen years from now, if we look back on the interim period, our definition of pharmacognosy will be dependent to a considerable degree on the research activity in the field that has taken place during that 15 year slice of time. Here again, the problem appears to arise because of the reluctance on the part of some researchers to make use of techniques in other and related areas and, in part, because of the lack of training to properly avail themselves of research opportunities and currents. There certainly is a need for a well-defined body of research going on in pharmacognosy which can show evidence of productivity in terms of modern drug needs.

It is disconcerting to note that from time to time significant research needs are evident in areas that at least border on pharmacognosy and yet no place in the United States is there

a pharmacognosist to whom people can turn for research programs and advice in such areas. A few years ago, when the U. S. Department of Agriculture decided to set up a program at one of its regional laboratories for the exploration of the possible stimulation of plant growth for drug use, after a survey of the colleges of pharmacy, departments of agriculture and other places, concluded that only by getting a team of agricultural experts and chemists could the job be done. The nature of the task was such that there should have been at least one pharmacognosist available for this project at that time.

At a time when it was necessary to explore the plant kingdom more thoroughly for the presence of steroids which could be potential raw products for important steroid medicinals, an exploration indicated that there was no one at the time in the United States in a college of pharmacy making a thorough study of the influence of species relationship and chemical structure.

There is a need for pharmacognosists to develop strong research programs that have objectives which are in keeping with broad objectives of research in related areas so that there will be well-defined experts in these fields when the occasion demands. I am convinced that there must be many problems worthy of a great deal of financial support if they are faced with realism and vigor and lack of concern about the necessity to borrow generously from related fields.

These are some of the broad problems that I have characterized as stemming from the need for the re-definition of the field of pharmacognosy.

The second group of problems seems to me to revolve around the question of teaching level. In the first place there appears to be a great deal of disparity from one school to another in the thinking about the location of pharmacognosy in the curriculum. I notice from the survey compiled by Dr. Crane, and this is in line with my own experience, that the majority of schools offer pharmacognosy as a Junior subject, but quite a sizable number offer it as a Sophomore subject and a few as a Senior subject. Obviously there is a tremendous difference between the outlook of pharmacognosy at the Sophomore level and at the Senior level. At the Sophomore level it is admittedly taught almost as an orientation subject to familiarize young pharmacy students, with inadequate science backgrounds, with the field of drugs using the naturally occurring drug as a base. It is either this, or what is often worse, it is an attempt to teach the pharmacognosy at a higher level than the

student's capacity to absorb it. It is hard to see how present day pharmacognosy can be taught before the student has had organic chemistry even though he may be taking it concurrently and perhaps the same should be said about microbiology, physiology and biochemistry, particularly. Now that we are moving to a five-year program, it would appear to be wise to advance pharmacognosy to the upper division uniformly and to adjust the teaching of it accordingly.

Related to this problem of the level of teaching of pharmacognosy is the question of what courses should be given before pharmacognosy or simultaneously with it. In discussing this problem with some of the pharmacognosy teachers, I find considerable variation in your reactions to this question. Quite a sizable number of pharmacognosy teachers feel that they cannot teach pharmacognosy adequately without the student having had at least one semester of biochemistry while others feel that it is inconsequential as to whether biochemistry is even in the curriculum or not. These questions revolve around courses other than chemistry courses, also. One pharmacognosy teacher expressed the opinion sometime ago that it was not necessary for the students to have had beginning zoology and botany as prerequisites while others have felt that even more advanced biological courses were, if not needed, at least more nearly ideal, if pharmacognosy is of moment. The question of what courses are pre-requisite or co-requisite is certainly tied to the level of the teaching of the pharmacognosy course.

A third problem in this category seems to me to be how pharmacognosy co-ordinates with the other professional courses. This again varies considerably from one school to another, some schools indicating that pharmacognosy is a field to itself and isn't particularly to be co-ordinated with pharmaceutical chemistry, pharmacology and the pharmacy courses. Others feel, rather strongly, that it is fed and nourished by some of the other professional courses and, perhaps even more important, it serves as a tool in some of the other related disciplines. I have always assumed that there is such a thing as thinking pharmacognostically and that if a person is taught to think along these lines properly, something of this discipline spills over into the area of dispensing, let us say, or into pharmaceutical chemistry and pharmacology. It is not enough, however, to say this is true, but I think there needs to be some rather definite avenues explored to assure its accomplishment. In doing this, considerable care has to be exercised in the area of pharmacognosy, because of the very historical nature of the discipline, to assure that the mythology and legend of crude

drugs are put in their proper perspective. Every now and then, pharmacologists and clinicians complain considerably because the student is unable to distinguish properly between alleged physiological properties of those drugs that I speak facetiously of being of the pipsissewa class. Physicians who ask the pharmacist for advice concerning drugs do not wish to be introduced to an infusion of buchu when they are asking for a change from a mercurial diuretic. And yet this is the kind of thing that sometimes happens, if care is not exercised in separating fact from fancy.

In the discussion of observations and problems up to now, we have been thinking of Pharmacognosy primarily as a scientific discipline which it is. At this juncture, I would like you to think for a moment about the fact that the pharmacist, and I am speaking not only of retail pharmacists but virtually all pharmacists, practices a kind of art based upon the use of his scientific knowledge. That the scientific knowledge is necessary is something that I would be one of the first to insist upon, but I wish to emphasize that there is a very definite problem in relating this scientific discipline to the art that constitutes practice.

The same is true of medicine. In selecting a physician, personally, I would insist upon one who has a very thorough understanding of scientific physiology, particularly, and certain other related disciplines as well. But secondarily, I want to be sure that the physician can relate this scientific knowledge properly, economically and effectively on the diagnosis of the peculiarities of me at the proper time and reach a competent **decision** as to what should be done.

Now we have this same problem in pharmacy and the pharmacist, regardless of his place of practice, often must call upon his knowledge of chemistry, biology and the various professional problem that is his at the moment. This professional problem may be solved by methods which are quite different from those of the bench scientist. Here, again, pharmacognosy is not alone in having this condition to meet. With the changing face of pharmacy and, as I see it that face will change even more in the future, it is necessary to take a hard look at many of our ideas concerning pharmaceutical curriculum making.

In the first place as we look at pharmacy in relation to the other health sciences, we find that the pharmacist's professional service is intimately bound to a commodity rather

than to what appears, at least to the recipient, to be a highly personalized service. We further this concept, also, because our scientific disciplines all point up the commodity character of the subsequent substance to be dispensed, namely, a drug or pharmaceutical preparation. One of the weaknesses, or at least a major problem causing aspect of pharmaceutical practice is the fact that we do not work closely enough with people. There is a need for all persons teaching in pharmacy schools to be aware of this situation and to be looking for possible solutions. We have conceived far too narrow a role for the pharmacist and one of the hopes of the new extended course is that by broadening the educational outlook of the pharmacist, we can broaden his profession ultimately as well.

Let me give a partial illustration of what I mean by recalling that, in a conversation with the Dean of a Medical School, he indicated that in his judgment, one of the most important functions of a teaching hospital is the teaching of the patient. He is insistent upon the dietitian, for example, teaching the diabetic and other patients needing special diets, exactly how to calculate diets, to prepare foods for special purposes and all of the other aspects of nutrition that are necessary for the patient to know. He expects similar teaching from the occupational therapist, the physical therapist and all of the other related paramedical personnel. He is eager for the hospital pharmacist to participate in this program because he believes strongly that the pharmacist has something of importance from his area of specialization to bring to the patient. I might add that he has not been too successful in getting this concept across primarily because he does not find enough pharmacists who are willing to undertake and press this important and rather novel conception of their duties. There are others, in the medical field, also, that are looking toward a modified conception of pharmacy and the pharmacist and his duties and it is up to us to put meat on the bones.

I am not certain where the specific area of pharmacognosy fits into this concept of pharmaceutical practice that is developing, but I am sure that it has a place and it is an important area for exploration and thought, transcending the purely scientific, for you who are teaching in this important academic field.

It has been said by many in many places and at many times that the pharmacist is too narrowly trained and that he needs much more non-science, non-professional teaching in his curriculum. This is one of the principles upon which the five-

year program is being developed. I would like to call your attention to the fact, however, that if about one-fifth of the new curriculum becomes general education, I am sure that this is the maximum that can be squeezed in and that this still is not as much general education as many thoughtful people would like to see. It seems to me that one of the ways to aid this situation is to teach all pharmacy subjects from a broader and more humane base than we have been inclined to do in the past. Pharmacognosy lends itself to a broad outlook because of the very nature of the field. You cannot avoid getting into discussions of the implications of world politics and perhaps even local politics on the movement of natural drugs to the market, for example. The legendary drugs are intimately tied in with religious practices and unique social customs outside of the predominating views of Western Civilization. Economics enters the picture very frequently when it becomes necessary to decide whether to grow a drug locally, whether to continue to import it, or whether to synthesize the active constituents. Geography, anthropology, and many other social sciences impinge upon pharmacognosy and can be brought into the teaching program in an effective and broadening manner. In fact, this is part of the meaning of scholarly teaching. And so, one of the important problems of the teaching of undergraduate professional Pharmacognosy is to broaden the outlook beyond the mere basic science outlook that is so obvious.

The next group of problems in pharmacognosy as I see it are the problems of professional pharmacognosy itself. The first problem is that of the background of the teachers in the field. A glance at the Crane report indicates that there are still a fairly large number of persons in this field without the Ph.D. degree or its equivalent and that there is relatively a large percentage of those who do not have their degrees in pharmacognosy. This in itself is not bad, in fact, I think it is rather fortunate excepting for the fact that in many cases this situation is present because the person is primarily trained in one of the other professional fields, is dividing his teaching time between these other areas and Pharmacognosy and owes greater allegiance to the other field. It is in this sense that the situation is weak because there are not enough full time teachers in the area of pharmacognosy who are properly trained and dedicated. While I have stressed that fact and wish to emphasize the corollary, namely, the need for more strong centers of graduate instruction in pharmacognosy, at the same time I would like to emphasize the need for bringing more specialized persons with training completely removed from pharmacy into our pharmacognosy teaching especially at the

graduate and research levels. There is a need particularly for plant physiologists, plant biochemists and related specialists whose contributions can be significant if the specialist is imaginative and adaptable to the needs of pharmacy. It has been my observation, not only with respect to pharmacy colleges but other places as well, that much of the real progress, from the scientific point of view at least, is made when persons well trained in one discipline learn the disciplines of another field and invade it with vigor. We could use a dozen or more strongly trained individuals from the natural sciences who will bring this kind of vigor to pharmacognosy.

I mentioned that we need more strong centers of graduate instruction in pharmacognosy. I am not so certain that we need more locations but we certainly need more strength. Related to this is the development of the graduate program of such a broad and thorough character that we can find plenty of distinct professional uses for a pharmacognosist outside of the teaching area. We need to have demand for such people, a demand beyond the product development area of the pharmaceutical industry and until we get that demand, again we will not have as strong a field in pharmacognosy as we would all like. I am sure that many of you are in a better position to judge where these vocational uses and opportunities lie and I hope that thought will be given to the importance of this.

Also, closely related to this point is the need for creating a distinct feeling of expertness in these areas so that the moment anyone thinks of plant science in any connection with drugs, he will immediately think of certain departments of pharmacognosy in a college of pharmacy for if such expertness is not in pharmacy where should it be?

There are many more observations that I could make relative to the current teaching of Pharmacognosy. I have not touched upon the pedagogical aspects of teaching which, incidentally, are no stronger or weaker in pharmacognosy than they are in other disciplines. Only lack of time caused me to eliminate this subject which is important, for I am certain you are all well aware of the need for better teaching in all of our colleges and universities.

I have not touched upon other problems which some of you feel are very acute because you are perhaps closer to them than I am. Many of these problems are at least mentioned in Dr. Crane's summary of the recently compiled survey of

pharmacognosy teaching and I am sure you will be stimulated to do a great deal of thinking about these things that are so well outlined.

I must apologize for being somewhat blunt about my observations, but I had the feeling you would wish me to be so. As I stated in the beginning, these problems, which are rather severe, are to be expected in all fields from time to time. I am sure that the vigor and the imagination of some of you teachers are going to go a long way to solving these problems and pharmacognosy will become the area again to which one can point with considerable pride in our colleges of pharmacy. Please believe that my criticisms and comments were meant in an attitude of friendliness and with an eye to the importance of having real strength and prestige in not only pharmacognosy but all of the areas peculiar to pharmacy. I hope that you have a most productive seminar and that you will all return to your colleges stimulated and with a feeling of determination to accomplish great things for your schools and your departments.

THE NEW PHARMACOGNOSY - WHAT IT IS AND WHERE IT IS GOING

Melvin R. Gibson

I'm very honored and pleased to have been chosen for this presentation following the distinguished gentlemen on this afternoon's program. I was charged by the chairman of the Seminar Committee to produce a "keynote" address. Dean Webster is very well aware from our close association that this may well turn out to be an "off-keynote address". For what I have to say about the present and the future of pharmacognosy will not be sugar-coated, will not even be palatable to some of you. It will, however, be what I think is a forthright appraisal of our present and future problems--the problems and challenges which contribute to making pharmacognosy what it will be tomorrow.

I'm going to divide my remarks into five categories: (1) course content, (2) methods of teaching, (3) facilities, (4) faculties, and (5) opportunities.

Course Content

Probably no other area in the pharmaceutical curriculum is more misunderstood than is pharmacognosy. There are those who teach pharmacognosy who don't seem to understand what it is, there are many pharmaceutical faculties who don't understand what it is, and to even greater disgrace, there are even deans who don't or won't recognize it for what it is. And I think the last word "is" is critical. Most of these people understand what it <u>was</u> but can't seem to make the transition to what it <u>is</u>. Pharmaceutical people have been able in their thinking to make the transition regarding the changes in pharmacy technology, pharmacology, and pharmaceutical chemistry, but not pharmacognosy. At least they no longer associate the strict area of pharmacy technology with conseals and cachets; they have come to think of pharmacology as no longer a branch of materia medica made up of the study of poisons and doses. People have come to recognize pharmacology as a vital science dealing with the action of drugs on bodies. Similarly, it is understood now that pharmaceutical chemistry is no longer a course in the memorization of properties of compounds and

stereotyped reactions; it is known as a course where structure-activity relations are learned. But pharmacognosy to so many people in pharmacy means only chasing stone cells under a microscope, memorizing botanical names, and learning about plant drugs which have decades ago lost their usefulness. What is the basis for this misconception? I think the misconception which persists regarding the course content of pharmacognosy is intimately related to the other four subtopics I shall cover. It's related to our methods of teaching, our facilities, our faculties, and our opportunities. And in each of these subsections I shall state or imply how aspects of these have contributed to the confusion which obtains in the minds of our colleagues in pharmaceutical education and in the rest of the pharmaceutical family.

Pharmacognosy as it exists in many minds seems to me to be like a dowager who, hit with inflation and no longer able to live on the interest of her capital, delves into the principal rather than investing in new growth stock. She prefers to base her future on that which she has had for so many years rather than that which has a future. In pharmacognosy too often people have clung to the teaching of drugs far longer than the value of the drugs justified; they have been reluctant to cast the old aside and either find a substitute or recognize a new area to encompass. They have been content to live on interest--the cursory facts about drugs--without investigating the basic tenets which are behind these facts or the coordinating theories which are the foundation for the scientific justification for their existence. The course content of pharmacognosy must be a skeleton, or skeletons, of fundamental information of current impact, not a mass of diverse epithelial tissue with no coordinating bodily structures. Further, the skeletons must be those which serve the purpose of the bodies today and tomorrow--not yesterday.

The drugs of plant origin should be taught as parts of vital systems, as substances which have common chemical and pharmacological applications. The characteristics they share in common are the skeletal structures on which are built the peculiarities of the individual members of the drug substances which are part of this segment of pharmacognosy. The skeletal chemical and pharmacological unifying principles are all-important. The differentiation of epithelial material (the peculiarities of the drugs themselves) is of secondary importance and should be of secondary academic concentration.

This area of pharmacognosy--the drugs of plant origin--is an important part, but only a part, of the totality which is pharmacognosy. And for many teachers of pharmacognosy this is the part of the dowager's principal which is being eaten away by changes in the world around us and which is all too often not being replaced by new material to keep up with the times.

We are faced with a very serious problem in pharmacognosy in that for too long we have been living on a dwindling capital of crude drugs. Why is this? Some will say the organic chemist has taken over; most drugs come from the organic chemists' laboratories. This is true. But think of the number of organic chemists who are at work all over the world synthesizing compounds and working on the vast complications of chemical reactions. How many drug plant chemists are there, or even, how many plant chemists are there? It's like comparing an atomic explosion to the pop of a cap pistol! And the United States' proportion of the pop is smaller than the leading European countries.

The problem is not that **most** new compounds come from chemists, but rather it is that too few people are trained to investigate plant substances, and particularly drug plant substances. You can't have new drugs of plant origin unless someone finds them. And if few people are looking, few will be found, obviously. There are thousands of drugs yet undiscovered in plant products, and they probably will remain so unless we concentrate more on the search. I shall come back to this under the fourth and fifth topics of my remarks--faculties and opportunities.

The dwindling supply of drugs of plant origin, then, certainly should and often does manifest itself in our course content. There needs to be a lesser amount of time spent discussing the individual drugs of plant origin. This must be done. And where it is not done, we in pharmacognosy leave ourselves open to justifiable criticism.

Contrary to the belief of some detractors of pharmacognosy, the subject does not begin and end with the drugs of plants of higher orders. By historic definition it deals with those drugs of natural origin. And to fill the void in our courses which is left by the dwindling capital of drugs from the higher plants come the tremendous areas of antibiotics, hormones, vitamins, enzymes, and biological products. Surely any modern

course in pharmacognosy must devote a large share of its time to these subjects. To do otherwise is a failure to reinvest capital. These are as much a part of pharmacognosy as anything can be. I recognize that in some institutions the pharmacognostic aspects of these topics are included in other courses of other pharmaceutical areas; it should not be. A properly trained pharmacognosist is most qualified to teach the pharmacognostic aspects of these subjects--antibiotics, hormones, vitamins, enzymes, and biological products. We are not in a position of grasping at new subjects to fill the pharmacognosy area, but rather it is a recognition of who is best able to teach the subjects and recognizing the progress and change which has occurred in the nature of modern therapeutic substances. Where these topics are wholly usurped by the areas of pharmacy, pharmacology, and/or pharmaceutical chemistry, often one finds the staffs of these departments looking down their noses at "obsolete" pharmacognosy because it only teaches of drugs of higher plant origin. The situation is like taking the food away from one member of the family and then smirking because he's starving to death!

You will notice that I have left out any mention of the areas of insecticides, herbicides, and rodenticides in discussing course content. This is intentional. In comparing the results of the survey circulated by this Seminar's Committee and compiled by Dr. Crane with the results obtained by Dr. VanderWyk in his survey in 1953, one finds there are about 50 per cent fewer schools which include these subjects in their pharmacognosy courses. It is my personal opinion that these subjects deserve minor consideration in a pharmacognosy curriculum. The subject matter involved certainly plays a minor role in pharmaceutical practice. I think they can be adequately covered in assigned reading or seminar presentations.

The course in pharmacognosy, then, must include the basic principles of higher plant substances and the facts peculiar to the individual drugs of these classes; it must include the pharmacognostic aspects of antibiotics, hormones, vitamins, enzymes, allergens, and biological products. All of us must be alert to the advances in drug therapy to recognize that in the pharmaceutical curriculum which can best be taught by us. What these advances will be it is impossible to predict. Another Fleming or another Salk may change the picture tomorrow, but rest assured pharmacognosy will still be a part of the picture.

Methods of Teaching

A great deal has been written about "how" pharmacognosy should be taught. In this aspect, as in course content, we have gone through a gradual evolution which I think is quite logical. To teach in depth one must have information in depth. Thirty or forty years ago not much was known about the chemistry of drugs or how they acted. But much was known about the botany of plants. To teach in depth then it was necessary to teach in botanical depth, hence the taxonomic approach to pharmacognosy. Today we know more about chemistry, and we know more about pharmacology. Today the more modern approaches are chemical or pharmacological because they more closely ally themselves with the approaches of the other areas of pharmacy than did the botanical. At the moment the chemical system seems to be the more popular. And I think this is logical. Whether rightly or wrongly our pharmaceutical curricula are still chemically rather than biologically oriented. I think we waste much paper and expensive print trying to convert one school of thought to another. I think it is generally accepted that the approach to pharmacognosy should be chemical or pharmacological. Which, I think is a matter of personal choice, a choice which probably will be dictated by background and training. As long as the pharmacy curriculum is chemically oriented, I think pharmacognosy will be largely chemically oriented. If the future demands of a pharmacist require that he be more of a biologist, possibly the trend will change, but in the foreseeable future I visualize the pharmacist as chemically oriented, a chemical orientation which has strong biological support. Hence, I predict the future courses in pharmacognosy will continue to be predominantly chemical in outline. Again I say, I think the choice is one for the instructor to make, and he should teach the course in whichever way he can teach it best. How will pharmacognosy be taught in the future? I hope we can say "well" and each pursue that end as he is best prepared.

Facilities

The facilities for teaching and research in pharmacognosy as found in this country vary from nothing to extensive. The capabilities for using these facilities have about the same range. Unfortunately sometimes the two are not in productive ratio. I think schools vary the greatest in graduate and research facilities, and relatively few seriously lack the

needs for an undergraduate program. Even the best facilities for pharmacognosy research in this country are inadequate. Dr. Schwarting in his article to appear in the summer issue of The Journal states as follows:

> It is urgent that pharmacognosy graduate education look seriously to the possibility of the establishment of an institute or center, within a university, where study and research can be pursued at the highest level of intellect and administrative understanding. Such an institution, through its permanent staff, visiting lectureships, and postdoctorate study would fill a void that would not only relieve the profession of the many attenuated graduate programs operating today, but provide the milieu in which the science can develop its highest potentialities. (1)

Thus Schwarting points up two needs for pharmacognosy--a facility for serious research in pharmacognosy and secondly, a strengthening of our faculties. I shall deal with the latter in a few minutes. But it does seem perfectly clear that as long as we follow the current trend of employing one or two pharmacognosists per institution, there will be little time for research and, hence, minimal facilities. In the Seminar Committee survey, out of fifty-one reports, twenty-seven schools had one pharmacognosist and fifteen had two. The pattern is very clear. I see little to indicate that the trend in the future will change materially. I heartily endorse Schwarting's suggestion that an institute be established which will be the pharmacognostic center in the United States. And I seriously suggest that this not be allowed to remain a suggestion; it should be taken up by some responsible group to be industriously pursued. I shall come back to this under faculties.

In this section on facilities we also should mention textbooks and laboratory manuals. In the Seminar Committee survey of fifty-nine schools, 80 per cent used two textbooks: Pratt and Youngken (13) and Claus (33). Nine schools used other texts. About two-thirds of the instructors using these texts indicated that they were satisfied with them. This observation coupled with the fact that seven different texts are used by only fifty-nine schools indicated to me that there is need for us to re-examine our pharmacognosy texts. I think in this respect pharmacognosy has been too slow in its evolutionary development. We have books which have a taxonomic

approach but bow in the direction of the chemical approach. We have a book with a pharmacological approach which has difficulty getting everything under the tent. We have a book which tries to classify all things chemically and ends up with some strange things under the same blanket. I think pharmacognosists should recognize that pharmacognosy is now a complex science, and we cannot hook together everything that is pharmacognostic and expect a book which has continuity. The only thing which holds the facets of pharmacognosy together is the biological origin. Hence, I think we should do as pharmacy technology has done - direct the subject matter into more than one book. Pharmacy technology has its books in beginning pharmacy, dispensing pharmacy, physical pharmacy, etc. I'm sure some of you can remember when all of pharmacy was taught from one book. If we in pharmacognosy are to have books which are scholarly presentations of their contents, I think we must recognize the necessity of keeping our texts within the bounds of consistency and logical content. If there are too many chickens under the hen some get cold. Some of the material "attached" in pharmacognosy texts leaves one cold--and wanting. For example, I should like to see a good text on biological products, and I should like to see a good text on vitamins and hormones. The coverage of these topics in our present texts is, to say the least, cursory.

I think the stature of pharmacognosy is very often judged by its texts. I do not think our present selection is worthy of what we should want pharmacognosy to be. I predict that the future will bring more specialized, more scholarly texts.

The laboratory manual situation is even worse. The Seminar Report shows that 67 per cent of those reporting use no published manual, but prepare their own mimeographed laboratory instructions and study guides. Less than 25 per cent use the most accepted manual of Tyler and Schwarting. It seems to me there needs to be a great deal of discussion among pharmacognosists as regards what should be taught in a pharmacognosy laboratory. When 67 per cent of the schools use their own material, the diversity of approach is obvious. I hope the future will bring a more acceptable **laboratory** manual, although it certainly won't unless some give and take and by logical reasoning solve the problem of what the laboratory should accomplish. I predict that the future will show a decrease of time spent in the laboratory.

Faculties

In the fifty-nine schools polled by the Seminar Committee it was found that twenty-one teachers of pharmacognosy were not trained to be pharmacognosists. I am not narrow-minded enough to say that to be a good teacher of pharmacognosy one must be trained with a major in pharmacognosy. However, I will say--the chances are better. Pharmacognosy has been the richer for people who have adopted pharmacognosy teaching as their vocation. The notable examples are obvious to most of you. But I sometimes think some of our colleagues are too quick to accept ready and cheap substitutes to handle the subject. This only pauperizes pharmacognosy and all of pharmacy as well. As I have already mentioned, pharmacognosy not only is a science of plants, but is a science which calls upon a rich background in chemistry, zoology, bacteriology, and pharmacology. Few, if any, training programs encompass such a diversity of academic pursuits, even within the field of pharmacy. Our pharmacy graduates are probably least prepared to go on for advanced study in pharmacognosy than in any area of pharmacy. I think the readiness to assign the courses in pharmacognosy to the last person who joins the faculty results from ignorance on the part of a dean and his faculty. To assign the job to a botanist without the strong chemical, biological, and pharmacological background is simply turning the back to some of the important areas of pharmacognosy. Both situations only can lead to further weakening of the teaching program in pharmacognosy and, hence, in all of pharmacy as well.

This tendency to look outside the pharmaceutical circle for people to teach pharmaceutical subjects can be a blessing, and it can be a curse. I always pray for deans to recognize the difference. I always pray for deans anyway--they all seem to need it so!

I recognize in some deans the almost frantic desire to "enrich" their staffs from allied areas of science. Sometimes they seem to take the attitude that anything is better than a pharmaceutically trained person. Some of these people leave pharmacy a better place for having been part of it. Most of them leave pharmacy better themselves for having been part of it. I know few who have become real champions of the profession. And sometimes this lack of esprit de corps can have lasting damage on the morale of a student body. It often does the reputation of pharmacognosy no good.

Not only does pharmacognosy attract a diverse group of instructors; its instructors instruct a diverse group of sub-

jects other than pharmacognosy. The Seminar Report shows that pharmacognosists teach twenty-seven subjects other than pharmacognosy or closely related subjects. To some this might indicate rather catholic abilities, to me it indicates pedestrian teaching. With most schools having one or two pharmacognosists on their staffs--and one is most common--this means a division of labor and interest of the pharmacognosist, a division which can only mean attenuation of quality.

There appears to be a need for stronger pharmacognosists who are better trained, who are capable of handling all of the subject material within the broad scope of pharmacognosy. Where weakness prevails, weakness will be preyed upon. If an institution has a pharmacognosist who is ill-prepared to teach biologicals, or one who is ill-prepared to teach hormones and vitamins, the pharmacognostic aspects of these subjects will out of necessity be taught by others on the staff who by their training and interests are not prepared to teach them. If it is to be a strong and respected course, pharmacognosy cannot be simply a course in crude drugs. It must stand firm on what it is and what it will be. The best interests of pharmaceutical education must be served and they are best served when the best trained persons are teaching that which they know the most about. And this is where a pharmaceutically-trained faculty member can stand his ground and know what he is talking about.

As for the future, I suggest that a firm organization of pharmacognosists set the standards of qualification for pharmacognosists and that these qualifications be made known to all administrators. We should not be too quick to clasp every wayfarer to our bosom and call him brother--he may well be our worst enemy and an enemy to what is best for pharmacognosy and for pharmacy.

And our own skirts are none too clean. There are pharmacognosists in this room who should not be here. The following is a quotation from Schwarting's Summer issue article:

> "The aggressive recruitment of graduate students to provide positions for graduate assistantship programs repeatedly lends itself to the enrollment of students of mediocre ability and potential as well as creating in some instances the graduate program itself." (1)

The enlistment of cheap research lackeys under the guise of graduate training is self aggrandisement through extensive publications and results in professional pollution of the lowest order. Yet it has been done and the guilty parties receive accolades instead of the censure they deserve.

On the other hand we have those individuals who surround themselves with the luxuries of their position at great expense to their institutions, produce little, and say, "I wouldn't advise anyone to go into pharmacognosy." These are the traitors to their calling and leeches on the blood of pharmacognosy.

We need more pharmacognosists, we need good pharmacognosists, and these will come only if we have pharmacognosists on our staffs who are respected by their colleagues and by their students, people who attract those persons of high qualifications as graduate students. Pharmacognosy cannot stand any more dilution by weak ill-prepared staff members of still-born Ph.D's. And this is something about which we must be concerned now, not tomorrow, or we will be like the family who didn't worry about the daughter until she didn't come home for breakfast--then it's too late!

And I turn again to the European solution as suggested by Schwarting, we are greatly in need of an institute to improve what we have in pharmacognosy and to produce the quality personnel we will need in the future.

Opportunities

As far as the job opportunities for pharmacognosy, the situation is quite paradoxical. We produce so few pharmacognosists, the market for them outside of teaching is almost nonexistent. Positions in government and industry which could legitimately be filled by pharmacognosists go to botanists and agricultural chemists, and they beget their own kind. I think here again pharmaceutical education fails to adequately sell its wares to government and industry. If we had the graduate pharmacognosists to place in other than teaching posts, there would still be a selling job to be done. I think this points up the great need of the American Association of Colleges of Pharmacy to have a permanent headquarters and a permanent secretary to actively work with government and

industry to keep them better informed about what pharmaceutical education is producing. In the case of pharmacognosy it is not a matter of finding jobs for pharmacognosists but rather a matter of educating government and industry that the jobs they are now giving to others could be more productively filled by pharmacognostically trained personnel. Again, if we had a research institute for pharmacognosy this could be an important factor in the selling program as well as a place to produce competent pharmacognosists.

Conclusions

That is pharmacognosy as I see it, as it is now, and as I think it will or can be in the future. We need a broadly based curriculum in pharmacognosy, we need an improvement in teaching quality, we need facilities for research and training, we need more dedicated and more capable faculties, and we need more job opportunities for our pharmacognosists!

I have nothing to say further and I shall, therefore, discontinue giving wordy evidence of the fact. I have made some predictions and I have expressed some hopes. The predictions have been made despite what Josh Billings said, "Don't ever prophesy; for if you prophesy wrong, nobody will forget it; and if you prophesy right, nobody will remember it." what I have said I'm sure is not new to most of you, but if I have caused you to think or pricked your conscience, I will wear the golden chamberpot of success with pompous dignity.

I hope the remaining days of the week will plant the seeds of new ideas and cultivate the crop of old ones so that six years hence at the next seminar when someone else looks over the field, he can say, "Progress has been made; the profession has been served."

Reference

(1) Schwarting, Arthur E., Am. J. Pharm. Ed., 23, 340 (1959).

PREREQUISITES FOR THE NEW PHARMACOGNOSY

Willis R. Brewer

In preparing this subject for presentation without the benefit of a preview of Dr. Melvin Gibson's illumination on Sunday of "The New Pharmacognosy--What It Is, etc., " I was faced with a need for making a statement of opinion on the nature of this development in order to justify any views presented on the subject of prerequisites.

For the purpose of considering prerequisites, pharmacognosy old or new consists of the course or the courses which, in general, ought to prepare the undergraduate to face his professional career with an up-to-date and comprehensive understanding of the pharmaceuticals which are plant- or animal-derived products. What is new in pharmacognosy these days is the changing nature of the approaches to the accomplishment of this general goal. These were described as "Suggestions Concerning the Teaching of Pharmacognosy" at the conclusion of our last seminar in 1953. They were formulated to meet a need which was observed and described by our very able counsellor, Dr. Lloyd E. Blauch, as a "prevailing confusion" concerning the objectives of the instruction in this field. Dr. Blauch held the clearing up of this confusion to be the key to the selection of the materials of instruction that should be used and the key to the determination of the principles around which the materials could best be organized. "Without such principles," said Dr. Blauch, "your courses are likely to be encyclopedic collections or conglomerates of facts and ideas rather than unified courses aimed at accomplishing sound educational objectives."

The suggestions were intended to meet these constructive criticisms, to eliminate the "prevailing confusion" surrounding the objectives of the teaching of pharmacognosy and to crystallize the principles around which the available materials of instruction could best be organized. These suggestions pointed out the new pharmacognosy as the "applied pharmaceutical science which deals with the biological, biochemical and economic features of natural drugs and their constituents," and as a science in which the "dynamic phases, which are physiological and biochemical in nature, should be emphasized in teaching the subject." It was recognizable in 1953 that this new pharmacognosy had already appeared in some institutions through the emphasis of the living, physiological and

biochemical aspects of plant and animal drug development and an accompanying de-emphasis of the histological and morphological considerations of drug sources. Now, although it is far from the purpose of this paper, I must confess amazement at the slow rate of progress we have made in changing our favorite field from the old to the new!

With the benefit of expert guidance, from the educational standpoint, on what we needed to do in pharmacognosy and with the presentation, six long years ago, of a set of suggestions which are as yet unchallenged by any clearer formulation of objectives, principles and methods, we still have not shed the old pharmacognosy in favor of the new in more than half of our colleges. This is evident from the survey conducted by Dean Webster's local committee and compiled by "F. A. Crane." The survey indicated that only 25 out of 59 of the returned questionnaires included among the aims and objectives of the course the "understanding of biosynthetic relationships or synthesis of natural drugs and products" and only 21 of the 59 included "principles of biological cellular synthesis." On the other hand, a great majority of the survey replies (49 out of 59) included the objective of identification of official and important non-official crude drugs. If this same proportion of the returns had also rallied around the objectives dealing with the "biosynthetic relationships" and the "principles of biological cellular synthesis" we could have hailed the maturation of the new pharmacognosy at this meeting and pointed to six years of progress in pharmacognosy instruction at the majority of the schools.

It would seem that the old pharmacognosy, which Dr. Blauch warned might be no more than "encyclopedic collections or conglomerates of facts and ideas" still may prevail in over half of our schools. Are there new suggestions or goals to be proposed at this seminar which would be more readily accepted and put to use by more instructors of pharmacognosy? If so, do they offer more promise in preparing the pharmacy graduate to solve the problems he will face in the next 30 to 40 years of professional service? Or did Dr. Blauch touch upon the heart of our problem when he said of the new pharmacognosy, "I would warn you, however, that if you accept it, it will put you on your mettle. Only teachers who are well grounded in the physical and biological science can handle the subject if that conception is to prevail." Is it our educational backgrounds that are insufficient and our personal inertia that is preventing

our improving ourselves? Our colleagues in the other disciplines in pharmacy are politely wondering. For the good of our graduates and the re-vitalization of the field of pharmacognosy, we ought to answer these questions before we leave this seminar. Our group confusion was evident to Dr. Blauch six years ago. The shame of a worse adjective--stagnant--may be our justifiable label at this meeting. We have already been so classified by inference among those who study and release data on the number of research papers that come from the various disciplines in pharmacy.

I believe I have made clear my opinion on the nature of the new pharmacognosy and can therefore comment on the prerequisites for it. My first thought was to ascertain whether our confusion over the objectives of instruction in pharmacognosy might also be reflected in a confusion over the scheduling of pharmacognosy and its prerequisites and corequisites. The Webster-Crane survey has presented us with enough facts to justify a statement that, to some extent, this is true. Dr. Blauch, at the conclusion of the 1953 seminar, noted that the position of our course in the curriculum was ideally as a "link in a well arranged sequence beginning with biology and chemistry and leading up to pharmacology and dispensing pharmacy." In the suggestions accompanying his evaluation, the scheduling of pharmacognosy was recommended for the third year of a four-year curriculum, preceded by courses in biology, microbiology, physiology, organic chemistry and biochemistry and succeeded by courses in pharmacology and dispensing. The recent survey indicated that 14 out of 59 schools offer the course in the sophomore year and 8 in the senior year. I do not believe in standardization of all curricula on one pattern, but these vagaries confound the principles of sound education.

The recent survey also lists for us the names of courses taken concurrently with pharmacognosy, those taken subsequently, and, in each case, the number of schools reporting that arrangement. In order to supplement the survey specifically, rather than by implication, with the names and incidence of all courses scheduled prior to pharmacognosy, a list was prepared from the current catalogues of 57 pharmacy schools which gave a preferred sequential outline of courses required for the degree. This list is as follows:

General courses required in 57 pharmacy schools prior to the study of pharmacognosy

General Inorganic Chemistry	57
English Composition	53
Algebra	50
Trigonometry	44
Organic chemistry	41
Botany	35
General Zoology	33
Economics	32
Qualitative Analysis	28
Biology	21
Physiology	19
Quantitative Analysis	18
Speech	12
Bacteriology	9
English Literature	8
History	8
Social Sciences	8
Anatomy	7
Humanities	6
Accounting	5
Political Science	5
Psychology	5
Logic, Philosophy, Ethics	4
Biochemistry	4
Public Health	3
Theology	3
Anatomy & Physiology	2
General Mathematics	2
Modern Language	2
Marketing	2
Sociology	2
Calculus	1
First Aid	1
American Literature	1
Business Law	1
Typing	1

Pharmacy courses required in 57 pharmacy schools prior to the study of pharmacognosy

General Pharmacy	42
Orientation	32
Pharmaceutical Calculations	22
History of Pharmacy	16
Inorganic Pharmaceutical Chemistry	12

Theoretical Pharmacy	8
Pharmaceutical Mathematics	7
Organic Pharmaceutical Chemistry	7
Pharmaceutical Microbiology	7
Advanced Preparations	5
Pharmaceutical Arithmetic	5
Pharmaceutical Latin	4
Drug Store Retailing	4
Quantitative Pharm. Chemistry	2
Qualitative Pharm. Chemistry	2
Pharmacology	2
Literature of Pharmacy & Science	1
Pharmaceutical Technology	1
Galenical Literature	1
Biopharmaceutical Chemistry	1
Physical Pharmacy	1
Pharmaceutical Economics	1
Medical Terminology	1
Jurisprudence	1
Household Products	1
Manufacturing Pharmacy	1
Pharmaceutical Bioscience	1

Obvious questions may arise concerning the following facts gleaned from the above list and the lists of concurrently and subsequently scheduled courses from the Webster-Crane survey:

Only 4 out of 57 schools schedule biochemistry prior-to, and only 14 out of 59 concurrent-with, pharmacognosy.

Only 16 of 57 schedule bacteriology or microbiology prior-to, and only 20 of 59 concurrent-with pharmacognosy. Fourteen of 59 schedule microbiology subsequent-to pharmacognosy.

Two of 57 schedule pharmacology prior-to, and 11 of 59 concurrent-with pharmacognosy.

Seven of 59 schedule dispensing concurrent-with pharmacognosy.

Seventeen of 59 schedule biochemistry subsequent-to pharmacognosy.

Three of 59 schedule the basic science, botany, in the junior year.

Under the Major Problems section of the recent survey, 13 of 59 replies indicate that neither organic chemistry nor biochemistry are offered in the entire curriculum.

It appears to be possible that our confusion over the objectives of what we are trying to do may only be exceeded by our confusion as to how to do it, a potential state of professional delinquency.

Dr. Raymond Vanderwyk published a "Survey of Pharmacognosy" in a 1954 issue of the American Journal of Pharmaceutical Education which reported on the number of schools scheduling organic chemistry and microbiology prior-to, concurrent-with or subsequent-to the course in pharmacognosy. This data, together with information from our local committee's recent survey shows that the scheduling, with reference to these two prerequisites, is generally improving as noted in the following table.

Scheduling of Organic Chemistry with Relation to Pharmacognosy

	Prior-to	Concurrent-with	Subsequent-to
1954	40 of 67 schools	22 of 67 schools	5 of 67 schools
1959	41 of 57 schools	none	none

(In 1959, Pharmaceutical Organic Chemistry is scheduled prior-to in 7 of 57 schools, concurrent-with in 39 of 59 schools and subsequent-to in 40 of 59 schools.)

Scheduling of Microbiology-Bacteriology with Relation to Pharmacognosy

	Prior-to	Concurrent-with	Subsequent-to
1954	22 of 67 schools	19 of 67 schools	23 of 67 schools
1959	16 of 57 schools	20 of 59 schools	14 of 59 schools

The 1953 seminar included excellent individual papers on basic prerequisites for pharmacognosy in botany, zoology, bacteriology, human physiology and/or anatomy and organic chemistry. In connection with the use of biology as compared with introductory offerings in zoology and botany, Dr. Deno pointed out the difficulty in getting a good balance from both plant and animal areas because of the background of most biology teachers. A source of difficulty may also lie in the level at which the biology course is taught. If it is presented in the liberal arts curriculum as a terminal course to satisfy the laboratory science requirement in that area, it probably should not even be considered as a possible substitute for separate offerings in the two fields. The same may be said of microbiology in some institutions in comparison with basic offerings available in bacteriology which lead to subsequent courses in immunology and serology. However, if the microbiology course is not terminal in nature and is offered on a high level, its broader coverage could make it more desirable than a strictly bacteriological study as a prerequisite to pharmacognosy.

Dr. Ewart Swinyard's comments at the Utah seminar, on the value of human physiology and/or anatomy in preparing the pharmacy graduate to aid local physicians in evaluating new drug products, are even more pertinent today than six years ago. Certainly we should be alert for opportunities to include all such courses as prerequisites to pharmacognosy in order that the level of instruction can be raised and the value of the course be increased for the students entering pharmacology in the following year. The same purpose could be served by scheduling elective units permitting a student to choose among such courses as statistical analysis, plant physiology and others which would not only serve to upgrade the level of our course but would serve the student well in the other pharmacy disciplines and in his professional activities following graduation. We have little need of seeking new prerequisites, however, because we have a sizable task ahead of us in incorporating into our curricula those which have already been suggested.

These comments have been presented with the full appreciation that within another two years, as the curricula of all the colleges are expanded to not less than five years over-all, most schedules will provide ample time for proper arrangements of most prerequisites. I believe that this should be one of the primary goals to be accomplished and

evaluated before the next pharmacognosy seminar is held in 1965.

The criticisms presented include not only my own school, but my self as well, and are intended to be constructive in nature and offered in humility, as it is written in the Good Book, "Inasmuch as ye have done it unto one of the least of these, by brethren, ye have done it unto me." Only by self study and self criticism will we, as pharmacognosists, merit the privilege of being self directing in the accomplishment of the future goals of pharmacognosy.

DISCUSSION

Albers: You can't assess pharmacognosy unless you consider the curriculum as a whole. We tried Pharmacognosy after Organic chemistry. Certain courses in pharmacy require Pharmacognosy as a prerequisite for those courses. Pharmacognosy can't wait too long or the student will never get through the Pharmacy curriculum. Unless we have a genuine production line we have no way of getting an ideal program. We now have a 2 plus 3 program--get basic things out of the way, then we can build a curriculum without a lot of artificial prerequisites.

Brewer: I feel that there are problems of definition here. there are schools that schedule Pharmacognosy directly following botany. I feel that parts of pharmacognosy can help in the teaching of botany, but those elements are hardly sufficient to justify calling botany Pharmacognosy. Looseness of thinking in our course descriptions even in catalogs leads to problems and confusion in making and interpreting a questionnaire.

Redman: I wonder if the curriculum we've been talking of today is the new pharmacognosy?

Brewer: My subject wasn't really the new pharmacognosy. It was on prerequisites and was based on conclusions of the 1953 seminar. I don't feel that the conclusions that can be drawn now are any better than those that were drawn at the conclusion of the last seminar.

Youngken Jr.: The figures indicate a lack of change in five years. A more significant change will come to our programs in the change-over to the five year curriculum. I would recommend that before our next meeting we take inventory of the changes in the next two years based on the coming five-year program.

ESSENTIAL TOPICS IN UNDERGRADUATE PHARMACOGNOSY

Edward P. Claus

There is no doubt that the six years since the 1953 Teachers' Seminar on Pharmacognosy and Related Subjects which was held at the University of Utah have borne the fruits of the educational advice planted at that meeting. Because the outstanding instruction of the Seminar faculty of 1953 did not pass unheeded, our present day courses in Pharmacognosy reflect teaching of increasingly superior quality. A lack of diversified textbooks and laboratory manuals in Pharmacognosy was evident at the Utah Seminar and offered a challenge to a number of authors who have since contributed to the literary needs of the field. The methods of approach to the subject matter varied with each contributor; hence, Pharmacognosy teachers now are able to select the instructional outline best suited to their purpose. This paper is concerned with course content and is planned to focus attention on the essential topics in undergraduate Pharmacognosy. Although the essential topics might meet with general agreement, the methods of approach will surely vary with the teacher, with the textbook he uses, with the time he finds available, and with the advantages or disadvantages of the physical plant at his college. Individual approaches to the implementation of these essential topics will be presented by Dr. Maynard W. Quimby and by Dr. Jack L. Beal in the two papers immediately following this.

Because of its inherent diversification, Pharmacognosy is a science which is difficult to confine to a standardized pattern. All of us will agree that any subject dealing with natural products used in medicinal practice, with substances obtained from such biosynthetic laboratories as plants and animals, and with materials gathered from the far reaches of the universe, poses a sizable problem. Each new series of medicating substances originating from the microbiological world widens the scope of the problem. Each new research investigation of hitherto unknown plant and animal sources enlarges the horizon of Pharmacognosy. Since research in our field is on the increase, who can foresee what newly discovered substance will be the outstanding therapeutic agent of tomorrow? A new anti-cancer drug might be isolated from plant or animal tissues being extracted in someone's laboratory at this very moment. In our rapidly changing world, what we may agree upon today as essential topics might in another six years be obsolete.

Regardless, we as teachers of Pharmacognosy must define the subject matter we wish to impart to our students.

The following quotation, taken from The Pharmaceutical Curriculum (1) by Blauch and Webster, refers to the place of Pharmacognosy, as one of the Biological Sciences, in the education of pharmacy students. It emphasizes the objectives of the course and the extent to which the subject matter is used by the retail pharmacist.

"Knowledge of pharmacognosy enables the pharmacist to discuss intelligently with the physician products of natural origin, their constituents, and their preparation and preservation concerning which he may be consulted. It increases the background of biological information the pharmacist needs in order to answer public queries. Adequate knowledge of the aspects of pharmacognosy that deal with the recognition of certain poisonous plants and their physiological action better qualifies the pharmacist to render service to the community in case of accidental poisonings. That portion of the subject which deals with economic factors under the sources, production and commerce of raw materials and isolated constituents obviously prepares the student of retail pharmacy for everyday dealings in the buying and selling of products whose market values fluctuate periodically because of these factors. Such are some of the immediate uses the pharmacist makes of the subject in his daily service. There are many others."

The many fine papers which comprise the proceedings of the 1953 Teachers' Seminar have stressed the chemical and biological relationships existing among drug products from plants and animals. It is obvious that a basic chemical consideration of natural drug products is essential to a proper understanding of their mode of action. Drugs which contain anthraquinone glycosides as chief constituents are recognized as having cathartic properties because of the particular pharmacologic activity of those constituents. Whether such drugs are studied under the heading "Anthraquinone-Glycoside Drugs" or "Cathartic Drugs" is irrelevant in determining the essential topics for the undergraduate course in Pharmacognosy. The main point is that these drugs: Cascara Sagrada, Aloe, Senna, Rhubarb and others be included among the topics. Similarly, Belladonna Leaf and Hyoscyamus are important drugs to be considered, and whether they are classified as "Solanaceous Drugs", "Anticholinergic Drugs", "Antispasmodic Drugs", or Tropane Alkaloid-containing Drugs" is immaterial so long

as they are included in the general instructional outline.

The undergraduate course in Pharmacognosy is probably one of the first courses in the five-year curriculum which requires the student to call upon his knowledge of the prerequisite basic biologic concepts. To develop in the student the proper understanding and appreciation for drugs of biological origin, the instructor must present a suitable introduction to the science of Pharmacognosy. Since Pharmacognosy is steeped in tradition and historical significance, the instructor should include a treatise on the evolution and development of the science and should offer information on the gradual emphasis brought about by the creation of the United States Food and Drug Administration and its impact not only on Pharmacognosy but also on Pharmacy in general. Finally, the meaning of the term "Modern Pharmacognosy" so ably presented by Dr. Melvin R. Gibson in his preceding paper entitled "The New Pharmacognosy - What It Is and Where It Is Going" should be revealed to the student.

According to a recent survey (2), the prevailing tendency among Pharmacognosy teachers today is to employ a chemical classification when discussing drugs and natural products. However, the value of a brief consideration of the taxonomic and morphologic systems of classification should not be overlooked since these classifications represent definite contributions to the study of plant and animal drugs from viewpoints other than that of the retail pharmacist. For the benefit of those students who may possess the ability and the desire to pursue graduate studies, the significance of relationships between phylogeny, taxonomy, and plant and animal constituents cannot be neglected. Similarly, morphologic comparisons and visual detection of adulterants may strike the fancy of those few students who wish to engage in drug evaluation and analysis whether qualitative, quantitative or microscopic.

A knowledge of the production of drugs for the commercial market including collection or cultivation and harvesting, as well as preparation for pharmaceutical use, is necessary to the student for a complete concept of the drug trade market. In expanding this knowledge, a brief discussion of the various types of constituents would be appropriate at this point. Extractions of alkaloids, glycosides, saponins, resins, and other important phytoconstituents in addition to methods of separating one constituent from another is basic information for the student of Pharmacognosy. Subsequent to this, if the

teacher wishes, he may consider crystallization techniques and ways of proving chemical structure in purified compounds.

Although certain analytical methods might well be utilized in laboratory procedures or demonstrations later in the course, it is appropriate to mention them when considering the manner in which crude drugs and their constituents are prepared for the pharmaceutical market. Chromatographic methods, electrophoretic methods, and infra-red spectroscopy deserve attention from the Pharmacognosy teacher as well as from the teachers of the Pharmaceutical Chemistry courses. Analytical instrumentation as applied to Pharmacognosy is still a relatively unexplored area. The final paper of this Seminar deals with "The Application of Instrumentation to Pharmacognosy" as it pertains to graduate education and will be presented by Dr. Egil Ramstad and Dr. Adelbert Knevel. Another paper on this program concerns "Chromatography and Electrophoresis in Pharmacognosy" and will be discussed by Dr. Tracey G. Call. Although these subjects are of special interest, they should be carefully considered by the teacher of undergraduate Pharmacognosy because intricate explanations will exceed the needs of the undergraduate Pharmacognosy student who expects to enter retail pharmacy.

Determination of moisture content, detection of insect and rodent infestation, procedures involving microsublimation, and quantitative microanalysis are intimately associated with drug evaluation but may be cited later by the teacher in his analysis of individual drugs.

No introduction to Modern Pharmacognosy is complete until the student has been informed of biosynthesis and its effects on the development of constituents in plants and animals. The thoroughness of such a topic will necessarily depend on the training of the Pharmacognosy teacher. In the absence of detailed chemical knowledge, the teacher nevertheless can point out possible relationships between photosynthetic by-products and the final constituents for which the drug is used therapeutically. The possible influence of precursors could be stressed here and numerous examples could be cited. For example, the addition of phenylacetamide or phenylacetic acid, when added to cultures of Penicillium notatum, increases the yield of penicillin. And again, the natural steroidal sapogenins found in the genera Agave, Dioscorea or Strophanthus, among others, are precursors for cortisone substitutes. The teacher can awaken an enthusiasm in his students by relating

some of the fascinating adventures surrounding the search for new plant products of this type.

Similarly, the relationships of constituents to the taxonomy of living organisms can serve as a stimulus for lively discussions. For instance, the presence of volatile oils in the members of the parsley family, Umbelliferae, is characteristic. But what are the circumstances by which the fruits of Conium (poison hemlock) and Cicuta (water hemlock) develop oily liquid alkaloids in addition to the volatile oil? Are these genera endowed with a particular type of biochemical reactivity or do they perhaps absorb or form substances which act as presursors? Why do other genera of this family lack this property?

General unanimity of opinion will doubtless prevail when it is suggested that essential topics in undergraduate Pharmacognosy include the various chemical entities comprising natural drug substances. According to an outline suggested in The Pharmaceutical Curriculum (1), products of natural origin used as drugs may be based on a chemical classification as follows: Those containing:

1. Carbohydrates: sugars, polysaccharides, derived carbohydrates
2. Glycosides: cardiac, anthraquinone, phenol, cyanogenetic, thiocyanate, pigment, saponin.
3. Tannins
4. Fats, fixed oils, waxes
5. Volatile oils
6. Resins, oleoresins, balsams
7. Dyes
8. Proteins: serums and vaccines, blood derivatives, allergens.
9. Alkaloids
10. Antibiotics
11. Vitamins
12. Hormones
13. Enzymes

The subject of Carbohydrates is extremely broad and encompasses a multitude of substances of considerable importance to Pharmacy. To introduce the student to the carbohydrates, the teacher will probably describe the photosynthetic process and the manner in which sugars and starches are produced, translocated and stored in plant tissues. The hydrolysis

of sugars and starches, presented by the Pharmacognosy teacher, is dependent upon the student having had a prior knowledge of organic chemistry; if the sequence of courses has not permitted this prerequisite, the teacher must provide a proper background for adequate comprehension. In presenting the subject of carbohydrates, in which such substances as monosaccharides, disaccharides and polysaccharides are discussed, official examples of these might well be cited. For instance, polysaccharides and derived carbohydrates such as gums, mucilages, hemicelluloses, celluloses and pectin, could be exemplified by naming and discussing official drugs representative of these categories.

Probably the amount of time spent by the teacher on any individual drug will depend on his particular point of view. It is my opinion that if the retail pharmacist is to serve as a "drug specialist," a function advocated by many educators, it is essential that he receive instruction in "drugs". The Pharmacognosy teacher should thus specialize in "drugs", particularly those of natural origin, as individual entities. Hence, when carbohydrates are considered and derived carbohydrates are to be emphasized, such official drugs as Acacia, Tragacanth, Sterculia Gum, Sodium Alginate, Agar, Chondrus, Plantago Seed, Pectin, Purified Cotton, Methylcellulose and Oxidized Cellulose should be stressed. At this point, prescription products and proprietary items such as Bassoran, Imbicoll, Agoral, Kondremul, Siblin, Metamucil, Konsyl, Kaopectate, Pectocel, Cellothyl, and Oxycel might be mentioned in emphasizing the direct correlation of Pharmacognosy to Dispensing Pharmacy.

Glycosides may be considered in a similar manner accenting the general characteristics of this class of constituents, the various products of hydrolysis and how drugs may be categorized using the aglycone moiety. Following each individual grouping, official drug examples might be mentioned and as much time as deemed necessary devoted to each. Again, whether or not Digitalis is covered under the heading "Cardiac Stimulant Drugs", "Cardiac Glycosides","Cardioactive Glycosidal Drugs", or "Steroid Drugs", the teacher certainly would include Digitalis and its derived and related constituents among the essential topics.

The same treatment should be accorded others in the list of recognized types of drugs. For example, fixed oils, fats and waxes (or as they are otherwise referred to as "lipids")

exhibit chemical characteristics which cause them to be employed in many different ways. The student should be conversant with the chemical constitution of these drugs in general and should be aware of the implications involved when a certain fixed oil is heated to facilitate extraction from the plant part or how its physical properties may be changed by hydrogenation.

It is unnecessary for me at this time to direct your attention to the manner in which the teacher can deal with all of the categories enumerated earlier. Suffice it to say that tannins, resins, alkaloids, hormones, enzymes and others should form a definite portion of the topics to be interpreted to the students.

As stated earlier, the classification which has been preferred by most teachers is that based on the chemical constituents of drugs and natural products. This paper does not intend to compare the relative merits of a purely biochemical system over any other. It is merely a matter of individual preference whether Streptomycin and Neomycin are classified with drugs of the Carbohydrate group as Oligosaccharides, and whether Bacitracin, Polymyxin and Tyrothricin are included with Drugs of the Proteid Group as Polypeptides, or whether these drugs, Streptomycin, Neomycin, Bacitracin, Polymyxin and Tyrothricin, are classed with others in "Antibiotic Drugs". Without question, drugs having antibiotic and antibacterial properties have a definite place among the essential topics in undergraduate Pharmacognosy.

Again, whether Antitoxins, Serums, Globulins, Vaccines, Toxins and Toxoids are listed with Drugs of the Proteid Group or whether they comprise a group labelled Immunizing Biologicals, these therapeutic agents should receive the consideration of the Pharmacognosy teacher. Of course, when the subject of Immunizing Biologicals is discussed, the materials should include the latest product information released by the pharmaceutical manufacturers and also by the medical profession. Oral Polio Vaccine and its advantages over Salk Polio Vaccine would represent recent information which students expect from their courses of study. A mention of the newly released quadruple antigen "Quadrigen" could be incorporated into this lecture as indicative of the modern trend of the teacher's material.

Since the majority of allergenic substances originate in the plant and animal kingdoms, the consideration of allergy and allergens falls within the subject matter of Pharmacognosy. This topic was discussed fully in the proceedings of the 1953 Teachers' Seminar previously mentioned. Types of allergens, how they may be avoided or eliminated, the preparation of allergenic extracts, methods of assaying these extracts, and specific details concerning inhalant, ingestant, injectant, infectant, and contactant allergens form interesting phases of this field. A discussion of the retail pharmacist's place in disseminating information about allergy, about antihistamine drugs, and about the advisability of the allergic individual to seek medical attention cannot be emphasized too highly. This is practical knowledge and instruction which both pharmacy students and retail pharmacists should find extremely valuable.(3,4)

Another specialty field of Pharmacognosy is that of insecticides and rodenticides. Despite the fact that many new synthetics have been developed for controlling destructive or annoying insects, mites, spiders, rats and mice, certain long-recognized plant substances have not lost their effectiveness and are still included in many formulae. Rotenone and the pyrethrins are efficient insecticides and deserve consideration by the Pharmacognosy teacher. Red squill and strychnine are useful rodenticides and should be discussed in turn. According to the teacher's interest and the time available, other substances in these categories and in those of the fungicides and herbicides may also be included in the discussions. Since the retail pharmacist distributes a considerable number of these products, they are worthy of observation.

The general scope of Pharmacognosy should be as broad as the subject matter permits. An analysis of the functions of Pharmacognosy in the pharmaceutical curriculum in your own school should be undertaken to ascertain how Pharmacognosy can best serve the student and eventually, the retail pharmacist. Is Pharmacognosy to act as a basic foundation for Pharmacology, Drug Assay, and Operative and Dispensing Pharmacy? Should it prepare the student for the problems involving natural products he will encounter in those courses? Does Pharmacognosy provide him with the means of knowing prescription products and proprietary items which are composed of plant and animal drugs or their derivatives?

A practical aspect of Pharmacognosy which undoubtedly could be strengthened is that which informs the student of the

specific natural substances comprising such prescription products as Lanoxin, Serpasil, Varidase, Tao, Fulvicin and Casakol. Although no course should become an instrument for the mere memorization of trade names, nevertheless a certain amount of correlation between natural substances and prescription items accentuates the usefulness of the course in the mind of the student. And, after all, what is the real purpose of the training a student receives in Pharmacognosy or, for that matter, in any course in the Pharmacy Curriculum? Can we agree that the fundamental concept of the educational program in Pharmacy is to produce intelligent and responsible retail Pharmacists? Since it is estimated that approximately 80 per cent of Pharmacy graduates enter the retail field, should we not gear our teaching to that 80 per cent? Inasmuch as the majority of those students who register for the undergraduate Pharmacognosy course eventually become retail pharmacists, some in their own stores, some in chain stores, some in professional prescription pharmacies and others in traditional neighborhood pharmacies, we must exercise discretion in selecting our subject matter.

We are not trying to make biochemists or plant physiologists out of pharmacy students; instead, we want them to possess an appreciation of the applications of the principles of biochemistry and plant physiology to the field of natural products. There is a happy medium which meets the needs of our undergraduate course in Pharmacognosy. As we develop our course material and as we plan our course syllabus, we should ask ourselves this question, "Are the topics I have chosen really the essential topics in undergraduate Pharmacognosy?

REFERENCES

(1) Blauch, L. E. and Webster, G. L., The Pharmaceutical Curriculum, American Council on Education, Washington, D.C., 1952.
(2) Results of Questionnaire Concerning the Teaching of Pharmacognosy, compiled by F. A. Crane, A.A.C.P. Local Committee on Teachers' Seminar, Univ. of Illinois, College of Pharmacy, June 1, 1959.
(3) Claus, E. P., What the Pharmacist Should Know About Allergy, J. Amer. Pharm. Assoc., Pract. Pharm. Ed., 14, 28-30, 1953.
(4) Claus, E. P., The Pharmacognosist's Contribution to the Field of Allergy, Amer. J. Pharm. Ed., 23, 259-263, 1959.

DISCUSSION

Redman: We have an obligation to our students to be systematic. We now proceed to mix up this system with two or three others--we don't do justice to anyone. We can't avoid a chemical system of classification. Serums and vaccines presented as such don't fit under a chemical classification. They might be considered under proteins, perhaps--but the chemical classification isn't complete enough to satisfy our needs. Neither is any other than I've seen. The Therapeutic classification seems to be the best since that's the way the drugs are used.

Claus: I haven't sponsored any one of them over the others.

Dodge: A parallel development might be pointed out in pharmaceutical chemistry. There were many differences of opinion. Drugs were classified by chemical structure, then changed to pharmacological reactions, then to therapeutic use. Eventually each worker will have to decide for himself which system best suits his needs.

Albers: Dean Claus has mentioned thirteen different topics that should be covered. I would like to ask how much time should be spent on e.g., Castor Oil, or on Digitalis, or on Acacia. When you get to Antibiotics--where can one find the time to give the students enough material so that they can classify them from bacteria and from the other fungi--and then go into the active physical and chemical construction. With the biological products such as tobacco, etc., what can one tell students other than echoing what is official? The time factor is involved in all of these.

Claus: The amount of time that could be spent in teaching any particular drug varies according to the importance of the drug. Each of us must find the place where pharmacognosy can best fit into our curriculum. Acacia should be discussed in pharmacognosy but should also be handled in Galenical pharmacy--it may be mentioned in connection with vaccines or bacteriology. Find out where your course can correlate with the total curriculum. We need a meeting of minds with our own particular faculties. Other people may be prejudiced but sometimes we are just as prejudiced. I don't believe that one system has complete advantage over the others. None is perfect. You should pick out the one

you wish and with which you can make your best contribution. Our best results will come from a meeting of minds between our department and that of the bacteriology, pharmacy and pharmacology departments. If we draw sharp lines between fields we lose some of our significance. The five year program should clarify many of these problems.

Ferguson: We have found that the use of slides in lectures and laboratory sessions makes it possible for us to reduce time for effective presentation. Students read the text before coming to class and use these visual aids in lectures and lab. This method is simple and efficient.

Call: I'm not now teaching and I can say some things teachers won't admit. We are influenced in what we do by the fact that our students are preparing for and will take state board examinations--many of which are far behind current times.

Dunn: Would Dean Claus include work on fungicides in his essential topics?

Claus: I think that fungicides could well come within the broad field of pharmacognosy. These are not natural products but are chemicals used in the control or elimination of living organisms--however, I don't feel that they merit more than an hour or two.

Koffler: How do you deal with overlapping between courses. I feel that a certain amount of overlapping between courses and disciplines is helpful.

Claus: I agree to an extent, but correlation is not always saying the same words even though the same general topics are considered.

Hewitt: Sometimes students forget in 20 minutes or several days, let alone a year, therefore I feel that oftentimes repetition is indicated.

Sciuchetti: We have been on the five year program for 2 years. We have faculty meetings when we can discuss these problems. The subject of antibiotics is first presented in pharmacognosy, different aspects are given in chemistry, still different ones in pharmacology and then in biological products. Each time a different approach is taken and the correlation of information for all concerned is desirable.

Hewitt: We would be much surprised to find how many departments cover an item. And we would also be surprised to realize the number of items that we assume others handle and are not handled at all. Such a topical analysis of your work would be well rewarding in covering the total curriculum.

AN INDIVIDUAL APPROACH TO THE PRESENTATION OF THE ESSENTIAL TOPICS

I. Based on the Taxonomic System

Maynard W. Quimby

Dr. Jack Beal and I are agreed that, in no way, will his presentation and mine constitute a debate concerning which of the various approaches to the teaching of pharmacognosy is best. I am rather certain that many of you will agree that the subject of "the best approach" or "the preferred approach" has been over-discussed in the past, (Please do not infer that this statement refers to any previous Teachers' Seminar.) often to the point of being ridiculous. It is my personal hope that, at no time during this teachers' conference, will the discussion revert to such time-wasting depths. I promise you that I will do my best to stay away from the making of comparisons.

In this presentation I hope to tell something of how pharmacognosy is presented to the undergraduate students at the Massachusetts College of Pharmacy. The title of this presentation will indicate to you the trend of the discussion. The subject matter is covered by lectures and by laboratory assignments. Written quizzes are given rather frequently. These cover the materials considered in recent lecture and/or laboratory assignments. Commonly about five of these written quizzes are given during a quarter ("term"). More extensive written examinations are required of the students at the end of each quarter. Rather moderate use is made of identification examinations at various times.

The presentation of nearly all of the subject matter in pharmacognosy is based upon a consideration of natural (related) groups. We do depart from this plan somewhat during a number of weeks when we consider the subject of "Harmful Plants". The sub-headings under this category (Harmful Plants) are:-

a. Dermatitis-producing plants
b. Plants whose pollens cause allergic reactions
c. Some plants that are poisonous when eaten

Even though the number of species considered in each of the

above groups is rather limited we still group related species together wherever possible. It hardly seems necessary to present a detailed discussion of the specific bits of information included in the consideration of these subcategories. I do want to state, however, that this part of the work is given early in the school year when plenty of living plant material is available. Students are introduced to a considerable number of harmful plant species in the field and in the laboratory. Living specimens of the following kinds of plants brought into the laboratory for study:-

Poison Ivy	-	Rhus radicans
Poison Sumac	-	Rhus vernix
*Primrose	-	Primula obconica
Common Ragweed	-	Ambrosia artemisiifolia
Giant Ragweed	-	Ambrosia trifida
Buckhorn Plantain	-	Plantago lanceolata
Jimson Weed	-	Datura stramonium

*Note: Obtainable from florist shops.

These are only a few examples of the number actually studied to a greater or lesser extent by the student.

Before laboratory work is carried out on these or other harmful plants we always plan, if possible, to lecture on the species being considered. The following outline may serve to give you some understanding of what is presented in a lecture on Poison Ivy.

ANACARDIACEAE (Sumac or Cashew Family)
Brief discussion of the family

Rhus species - Sumacs

1. A number of white-fruited species belonging to this genus (Rhus) are capable of producing severe cases of dermatitis.
2. Red-fruited species, R. glabra (Smooth Sumac) R. typhina (Staghorn Sumac), R. copallina (Dwarf or Shining Sumac). and R. aromatica (Fragrant Sumac) do not cause such a condition.
3. The white-fruited species are woody, as are the red-fruited ones.
4. They vary in habit from small erect shrubs to vines, to larger shrubs, or to a small tree in a few cases.

5. All of these plants contain a resinous, oily material presumed to be the cause of the skin eruption.
6. The following species will be considered --
   a. Rhus radicans
   b. Rhus vernix
   c. Rhus verniciflua (source of a lacquer)
7. A closely related plant, Metopium toxiferum (Rhus metopium has caused trouble at times.

Note: Each of the above is discussed to a greater or lesser extent.

Poison Ivy -

1. Common names -- Poison Ivy, Poison Oak, Poison Creeper, Three-leafed Ivy, Picry, Mercury (Marcry, locally in rural New England).
2. Nomenclature --
   a. Various scientific names have been applied to forms considered by some to be distinct species.

R. radicans	R. diversiloba
R. toxicodendron	R. rydbergii
R. quercifolia	R. microcarpa

   b. Whether or not there are a number of distinct species is not important to us in this course.
   c. We shall use the name R. radicans in a broad sense to include the different variants.
   d. While this may not be botanically correct it will serve our purposes very well, as long as you keep in mind the sense in which this scientific name is being used.
3. Characteristics -- Even the form or forms found growing in the northeast vary considerably in habit.
   a. Constant features --
      i. stems woody.
      ii. leaves trifoliate (explain).
      iii. leaves alternate on the stems.
      iv. flowers in axillary panicles.
      v. flowers pentamerous and whitish.
      vi. fruits nearly globular, almost dry, and white or cream-colored, or dirty gray
      vii. rhizomes (rootstocks) horizontal and running beneath the surface of the soil for several meters in many cases.
      viii. rhizomes sending up new shoots at nodes.
      ix. Poisonous material present in all parts of the plant (pollen excepted).

b. Variable features --
   i. plants may be small erect shrubs or vines climbing by means of aerial roots on rocks, fences, trees, etc.
   ii. leaflets glossy or dull.
   iii. leaflets glabrous or somewhat hairy.
   iv. margins of leaflets entire, coarsely toothed, or even lobed.
   v. young leaves somewhat reddish in spring.
   vi. mature leaves definitely red or yellow in fall.

4. Habitats (environments) --
   a. Old fields and pastures.
   b. Along fence rows, often among growths of bushes.
   c. Along stone walls and edges of streams.
   d. In other waste places.
   e. In rich alluvial woodlands. (Explain).

5. Conditions of Poisoning --
   a. Some persons claim immunity. Discuss.
      i. this probably unwise.
      ii. susceptibility a matter of degree and probably no one is absolutely immune.
      iii. degree of immunity varies with--condition of the individual, condition of the plant, and circumstances.
   b. How contracted --
      i. by direct contact with the plant (fresh or dry).
      ii. without direct contact with the plant--
         From clothing, shoes, or implements used around Poison Ivy.
         From smoke. (Explain)

6. Symptoms of Poisoning -- usually appear within from 12-24 hours after contact, but may vary from a few hours to several days.
   a. Inflammation and swelling.
   b. Intense irritation and swelling.
   c. Vesicles or blisters containing a watery fluid.
   d. In more severe cases the vesicles coalesce and form large pustule-like swellings.
   e. Content of these may be pus-like in severe cases.
   f. Blisters break and, upon drying, scabs or crusts form over the affected surface.

7. Treatment --
   a. Preventive measures --
      i. learn to recognize the plant and keep away from it.

ii. after contact with the plant and before symptoms have appeared wash the affected parts with a 5% solution of Ferric Chloride in 50% alcohol.

iii. strong laundry soap -- discuss its application. Before going into a place where you are likely to contact the plant wash with such a soap and leave the lather on the arms and hands. OR After coming in contact wash thoroughly with this soap and rinse carefully with clear water.

iv. potassium permanganate solution (5% aqueous) applied after contact and before symptoms appear is used.

v. avoid contact with towels, face cloths, clothing, etc. used by afflicted persons, who may still have the oily, irritant material on their skin surfaces.

vi. avoid contact with implements which have come in contact with Poison Ivy plants.

b. Curative or Remedial measures --

i. many remedies have been used and suggested - Ferric Chloride Solution, 5%; not to be made from the tincture.
Calamine Lotion
Potassium Permanganate Solution, 5% aqueous etc.
Numerous others. See literature. A number of proprietaries. (Avoid using oily preparations as lotions or soaps until the poisonous constituent has spent itself!)

ii. antigenic preparations; discuss their uses.

iii. with cases that are at all severe consult a physician.

8. Eradication -- of Poison Ivy Plants --
   a. Hand grubbing. (Caution.)
   b. If in fields mow, plow, and harrow. Plant a cultivated crop. Discuss
   c. Chemical control: -- Discuss
9. Sources of Information -- Discuss
10. Plants Sometimes Confused with Poison Ivy -- Discuss

SPECIAL POINTS

1. In making up an aqueous solution of Ferric Chloride for use in treating Poison Ivy dermatitis always use crystals of $FeCl_3$.
2. Do not use the official Ferric Chloride Tincture of the N.F.

3. Do not use the N. F. Ferric Chloride Solution
4. These preparations are too acid and will irritate the condition.
5. Do not add HCl to the Ferric Chloride Solution intended for treating the dermatitis. Even if the solution is cloudy do not be concerned about it.

The following might serve for use in carrying out laboratory work on Poison Ivy.

Rhus radicans L. (Anacardiaceae) - Poison Ivy

a. Examine herbarium sheets, preserved specimens, and/or fresh material of this plant in a leafy condition. (Handle these materials carefully in order to avoid contracting a dermatitis.) Study the characteristics of this plant carefully and become thoroughly familiar with its appearance. Note the woody stems which, in many cases, show the presence of aerial rootlets. Examine material representing the creeping rootstock (rhizome) which sometimes grows horizontally underground for several meters. Is there evidence of shoots (branches) from the nodes of the rootstock?

Trifoliate leaves are characteristic of this plant. The leaves are borne in an alternate manner along the aerial stems. Note that the three leaflets may differ considerably in several respects. They may be glossy or dull green, glabrous or somewhat hairy. Observe these features, and also note that the margins of the leaflets are entire, toothed, or even lobed in some cases.

Flowers are perfect, with five yellowish-green petals. They (the flowers) are borne in slender axillary panicles. On certain specimens note the clusters of almost dry, nearly globular, white or cream-colored fruits (drupes). Each drupe contains a grayish, striped, one-seeded stone. Examine one of these stones that has been removed from a fruit and placed on the stage of a dissecting microscope.

Prepare a full-page drawing of Poison Ivy and label the structures underlined in the above paragraphs.

How does the habit of this plant vary? What is the arrangement of the compound leaves on the stem? What is the color of the fruits?

b. Examine herbarium sheets and living materials of certain plants that are sometimes confused with Poison Ivy. Record the names of several of these species.

c. Examine the display of commercial preparations intended for use in preventing and treating Poison Ivy dermatitis and become familiar with their names and the names of the manufacturers. Take particular notice of the composition and method of use of each product. Record the information as indicated by the instructor.

d. Enumerate at least five characteristics of the Poison Ivy plant which are considered to be constant for the species.

e. Examine the references and other forms of printed material made available in the laboratory.

f. List the authors, titles, and sources (publishers, etc.) of at least five of these sources of information.

g. Before the next written quiz carefully study your lecture notes on Poison Ivy, Poison Sumac, and other species of Rhus.

Appropriate procedures are followed in carrying out work on other "harmful plants".

As has been stated earlier all other materials taken up in our presentation are considered by natural groups, usually families. Obviously, in our courses, the students are not required to learn the name of every family from which a medicinal, pharmaceutical, or other economic material is obtained. Nor is the student required to memorize the biological characteristics of every family. College professors are usually reasonable people and we do not see why we should not be reasonable along with the great majority. On the other hand, we do put varying amounts of emphasis on certain selected families. Without some understanding of the characteristics of a plant family the student certainly cannot gain much of an understanding of a species within that family. After all, in presenting the subject matter of pharmacognosy as we do, the important or basic "unit" is the individual plant species. Here again of course neither the student nor the teacher should be expected to memorize description after description of plant species. Nor should there be an arbitrary list of points about a drug-yielding plant that students are required to

memorize. Certainly nothing could be more absurd in this day than to require that students memorize the biological origin, synonyms or common names, parts used, species and drug descriptions, histologies, etc. for drug after drug in endless numbers.

A happy medium must be struck, and of course teachers know that what appears to be a happy medium to the professor does not always seem to be a happy medium to the undergraduate or even to the graduate student. I've noticed that such a variation in opinion is not peculiar to pharmacognosy either.

Obviously the teacher must be the one to decide how detailed a consideration is to be made of a particular plant, or of the drugs or other materials obtained from it. The teacher must also keep an open mind and always reserve the right to change his mind. I guess we all learn this sooner or later.

Now to get back to the subject at hand. We have just mentioned that we do study the characteristics of certain plant families in some detail. Obviously the amount of detail will vary from group to group. Certainly there are many things of importance to be learned about plants of such families as the Pinaceae, Gramineae, Liliaceae, Rosaceae, Leguminosae, Apocynaceae, Loganiaceae, Umbelliferae, Labiatae, Solanaceae, Scrophulariaceae, Rubiaceae, and Compositae. The points to be learned here may not all be of medical, pharmaceutical, or chemical importance, but they certainly may be important as parts of one's education.

With such a thought in mind we should like to consider briefly one of the plant families covered in undergraduate pharmacognosy at the Massachusetts College of Pharmacy. For this purpose I have chosen the Nightshade family. We probably all agree that the Solanaceae are of importance for many reasons. The following outline may serve to illustrate how we might present these family characteristics during lecture time. Please remember that the lecturer can make this presentation as detailed or as simple as he wishes. We try to strike that "happy medium" mentioned earlier.

SOLANACEAE - The Nightshade or Potato Family -

Size - approximately 85 genera containing a total of about 2000 species; distribution world-wide.
Distribution - species fairly common in temperate regions, but much more abundant in tropics.

Plants - herbaceous for most of our species in this climate; those of warmer regions often somewhat woody and shrublike. Plants often possess peculiar odors.

Stems - commonly contain internal phloem.

Leaves - alternate on the stems; nearly always simple; contain internal phloem at least in larger portions of midribs.

Flowers - most commonly 5-merous (i.e. 5 sepals and 5 petals). Less commonly the sepals and petals each 4 in number; flowers regular (EXPLAIN).

a. Sepals - commonly 5 in number and at least partially fused together; usually forming a persistent calyx (EXPLAIN).

b. Petals - commonly 5 in number and fused to form bell-shaped, tubular, to funnel-shaped corollas. (EXPLAIN).

c. Stamens - 4 or 2 in number, and in pairs.

d. Pistil - bicarpellary and with superior ovary.

Fruits - characteristics important in identification work: - Many-seeded and of two general types; usually with persistent calyxes. Explain, using fruit models.

i. Capsule - produced by Tobacco, Stramonium, Hyoscyamus, etc. (Hyoscyamus fruit a pyxis.)

ii. Berry - Belladonna, Tomato, Potato, Egg Plant, Green and Red Peppers, etc.

Active constituents - most of them are toxic alkaloids.

Some Microscopic (Histological) Features -

a. Microcrystals commonly present; sometimes called "crystal sand". Explain microcrystals.

b. Other types of calcium oxalate crystals are also present at times. (Discussed in Textbook.)

c. Internal phloem in stems and leaves.

d. Glandular and nonglandular hairs commonly present.

Economic Importance -

a. Food Plants - Potato, Tomato, Egg Plant, and Green and Red Peppers.

b. Tobacco - Nicotiana tabacum and its many cultivated varieties are probably of more importance, from the point of view of dollars and cents, than any other single species of solanaceous plant.

i. Used in many tobacco products such as cigarettes, pipe tobacco, cigars, snuff, and chewing tobacco.

ii. Tobacco waste is the source of the alkaloid nicotine (liquid), commonly used as an insecticidal material. (Black Leaf 40 is a common commercial product containing nicotine (nicotine sulfate, 40%).

Notice - Nicotine is also obtained commercially from other species of Nicotiana.

c. Weeds and Poisonous Plants -
The Belladonna plant grows as an "escape" (explain) in some countries, especially England. Children have been poisoned from eating the fruits of this plant.
Stramonium, commonly known as Jimson Weed, is a common weed and poisonous plant in many parts of the United States and is a menace to grazing animals, etc. Other less well-known species from this family also fall into this category. Discuss selected examples.

d. Condiments - Red Pepper or Capsicum the best example.

e. Ornamentals - Petunias
Ornamental Nicotianas
Chinese Lantern Plant
Angel's Trumpet, a species related to Stramonium.

f. Medicinal Plants.

After such didactic consideration the student carries out a certain amount of laboratory work dealing with the Solanaceae. The following will serve to illustrate parts of such a laboratory assignment.

SOLANACEAE (Nightshade Family)

Suggested Materials Illustrating Certain Characteristics of the Members of the Nightshade Family

a. Carefully examine growing plants, herbarium materials, and other specimens of a number of members of the Solanaceae. Make use of information contained in your lecture notebooks and textbook. Prepare full-page drawings of one or more species. Use proper terminology and label all parts. Indicate the scientific name or names of the species represented.

b. The aerial stems of most medicinal species from this family are essentially non-woody, even though they commonly contain

rather well developed xylem regions. The presence of microcrystals in some of the parenchyma cells. (Other types of crystals may also be present.) Examine a portion of a fresh or preserved stem of one of these plants. Observe one of the cut ends of this segment under a handlens. Are definite regions evident to you? Cut a number of thin transverse sections and transfer them to a dish containing a small amount of alcohol. Select two or three of the thinnest sections and mount them in phloroglucin-HCl on a clean microscope slide. Add a cover glass and examine these sections microscopically. (Stained and permanently mounted sections can be used in place of temporary sections.) Make a careful anatomical study, locate and identify all tissues, their components and contents, and prepare a diagrammatic drawing to illustrate the structure of the stem. Representative portions or cells should be drawn in detail. Label.

c. By using epidermal strips and scrapings from the aerial stem make a study of the types of epidermal hairs possessed by the species being studied. Prepare temporary mounts in water of KOH solution. Locate and study the structures (epidermal hairs) microscopically. Prepare accurate drawings of as many types of hairs as possible. Label. Include the scientific name or names of the species studied.

d. Studies of leaves will be made when specific solanaceous drugs are considered.

e. Flower structure is very important in determining the identity of plants. Refer to the floral characteristics for the Solanaceae as outlined in your lecture notes.
   1. Determine the external characteristics of a fresh or preserved solanaceous flower. Prepare an enlarged drawing to illustrate its appearance. Label and include the scientific name of the species concerned.
   2. Dissect the flower and examine the parts carefully. Prepare drawings to illustrate the characteristics of the various parts. Again refer to your lecture notes and the Textbook for labeling information. Identify by scientific name.

f. Fruits of solanaceous plants are of two general types, namely capsules (Datura, Nicotiana, Hyoscyamus, etc.) and berries (Atropa, Solanum, Capsicum, Lycopersicon, etc.). After studying the following fruit types, enter the answers to these questions in your laboratory notebook. Of how many carpels does each fruit consist? Are seeds few or many?

How does the fruit of Hyoscyamus differ from most capsules?

1. Examine a solanaceous capsule and observe its various features. Locate the persistent calyx, valves, sutures, and dissepiment, if such are present. Draw (X1) and identify by scientific name. Label.
2. Make a careful examination of the berry of Atropa belladonna or of a similar fruit of some other solanaceous species. Prepare a drawing (X2) to illustrate its external appearance. Label the berry, persistent calyx, and pedicel.
   Make use of a sharp razor blade and cut transversely across this fleshy fruit about midway between the base and tip. Examine the cut surface of the lower portion and locate the pericarp, dissepiment, and seeds. Prepare a drawing (X2) and label.

I doubt if our lecture presentations differ very much from those of other teachers of the subject. Of course each individual has his or her own personal peculiarities or mannerisms, and no two persons are exactly alike, thank goodness. However, I expect that the "jokes" and the incidental trivia brought forth by the teacher during lectures, and at other times are pretty much the same across the country as well as elsewhere. And I feel sure that student reaction doesn't differ a great deal from place to place. You're probably as familiar with it as I am.

With us the students soon find that the taking of lecture notes is a pretty important practice. Open textbooks are not permitted during lectures and, at times, we even discourage students from bringing textbooks to lectures. (Of course books are required during laboratory periods.)

When we come to the presentation of lecture material on a particular group of drugs the detail into which we go varies from drug to drug. This of course is to be expected. Ergot, Penicillin, Digitalis, Rauwolfia, Belladonna Leaf, and various others are covered in more detail than are many other drugs that we might mention. For certain drugs we do present a considerable number of details concerning the species from which the drugs are obtained. As mentioned earlier in this paper we have no arbitrary list of points that a student must learn concerning every item considered. We do expect that scientific names of species will be learned in a considerable number of cases. The learning of some common names or synonyms is also required.

Detailed plant descriptions are presented to a very limited extent. However, some consideration is given to the characteristics of the plants in many instances. Morphological features, both macroscopic and microscopic, are covered to a relatively modest extent.

Students are expected to know the names of active constituents of particular drugs and to be familiar with certain physical and chemical characteristics of these constituents. General uses and the categories of various drugs, of their preparations, and of their derivatives are presented. Students are held for definitions of the many therapeutic terms used here. Names of important official preparations and derivatives are required. Other information concerning certain of these may also be expected. A considerable amount of posology is included. We believe that students will learn doses more readily when they are in close contact with the drugs, preparations, and derivatives than at any other time.

In some cases other points are introduced in reference to particular drugs or other biological materials. An example would be historical material concerning such drugs as Digitalis, Penicillin, Belladonna, Rauwolfia, Cinchona, and others. Some information dealing with the toxicology of certain poisons is given along with the other lecture material.

We plan to cover particular subject matter in lecture before assigning the same material to be worked upon in laboratory. We're not 100% successful in doing this but usually we manage reasonably well. The following sheets of directions may serve to indicate to you some of the work that might be carried out during one of our laboratory periods.

Suggestions for Laboratory Study of Selected Solanaceous Crude Drugs and Related Materials

SOLANACEAE (Nightshade Family)

Part 1

Belladonna Root and Belladonna Leaf

a. Become thoroughly familiar with the external characteristics of the Belladonna plant. Refer to information in your lecture notes and Textbook, and make a careful study of fresh

and/or pressed specimens of this plant. Observe preserved or fresh root systems if such are available in the laboratory. Enumerate the descriptive features of this plant in your laboratory records if such material is not already included in your lecture notes.

b. Observe and record the characteristics of the drug Belladonna Root. Refer to your lecture notes, the textbook, or the official monograph for descriptive information.

c. Examine transverse sections of this root microscopically. For this study, hand-cut sections in temporary mounts will probably prove to be more satisfactory than stained and permanently mounted sections. Proceed with this work under the instructor's guidance. What microscopic characteristics aid in distinguishing between young and old roots? Prepare labeled drawings according to the directions given at the time.

d. Observe and record the characteristics of the drug Belladonna Leaf. What part or parts of the plant constitute this drug? Record. Refer to the proper sources for descriptive information.

e. Examine and draw an entire leaf of the Belladonna plant (pressed or fresh). Label. The leaf of Phytolacca (Pokeweed) sometimes occurs as an adulterant in Belladonna Leaf. Examine an entire leaf of this adulterant and notice how closely it resembles the leaf of the Belladonna plant. Draw the Phytolacca leaf. Label.

f. Carefully examine all of the laboratory display materials pertaining to this assignment. Take particular notice of the displays of prescription specialties and other preparations, as well as of the literature. Record in your notebook information as indicated by the instructor in charge of the laboratory.

Part 2

Preparations and Derivatives of Solanaceous Drugs

a. Examine the containers of official pharmaceutical preparations, as well as the alkaloidal derivatives and their salts on display in the laboratory. Observe the physical appearance of each. Make certain that the names, uses, and

official doses of these materials are recorded in your lecture or laboratory notebooks.

b. Identification Tests. Perform and/or observe the results of the following official identification tests. Outline the procedures and state the results in your laboratory notebook.

1. Atropine, N. F.
   A. To about 10 mg. of Atropine contained in a porcelain dish, add a few drops of fuming nitric acid, and evaporate to dryness on a water bath: a yellow residue is obtained. To the cold residue add a few drops of alcoholic potassium hydroxide T.S. and a fragment of potassium hydroxide: the mixture is intensely violet in color (hyoscyamine and scopolamine, similarly treated, produce the same color as Atropine, but the presence of other alkaloids obscures the color effect).
   B. To a solution of Atropine (1 in 50) in diluted hydrochloric acid add gold chloride T.S.: a lusterless precipitate is produced (hyoscyamine similarly treated yields a lustrous precipitate.)
2. Atropine Sulfate, U. S. P., also responds to the above tests.
3. Scopolamine Hydrobromide, U. S. P.
   A. To about 1 mg. of Scopolamine Hydrobromide in a small porcelain evaporating dish add 1 drop of fuming nitric acid, and evaporate to dryness on a steam bath. Cool the residue, and add 2 drops of alcoholic potassium hydroxide (1 in 10): an intensely violet color is produced.
   B. To 1 ml. of a solution of Scopolamine Hydrobromide (1 in 20) add a few drops of chlorine T.S., and shake the mixture with 1 ml. of chloroform: the latter assumes a brownish color.

MORACEAE (Mulberry Family)

Cannabis sativa L.

a. Cannabis sativa, the plant from which Marihuana is obtained, is a tall, dioecious, herbaceous annual. Examine herbarium sheets and other materials of this species. Notice that the stems are coarse and rough. The leaves are either opposite or alternate, and palmately-compound in most instances. The 3-7 leaflets are narrow and have coarsely toothed margins. Prepare a full-page drawing of a nodal region of the stem with a single compound leaf attached. Label.

b. The flowers of Cannabis are imperfect. Examine material representing both the male (staminate) and the female (pistillate) plants. Notice that the staminate flowers occur in branched axillary clusters and that each flower consists of five perianth segments and five stamens.

c. The pistillate flowers occur in spike-like clusters. Each of these flowers has a solitary pistil which later develops into a fruit (achene, "hempseed"). Further, each flower is enclosed within a bract which later surrounds the achene. On these bracts are found non-glandular and glandular hairs. The latter contain a resinous material in which is found the active principles of Cannabis.

d. Make scrapings from several bracts into a drop of 5% potassium hydroxide solution. Examine microscopically and draw several of each kind of hairs. The "tongue-shaped" glandular hairs possess a multseriate stalk and an 8-16 celled glandular head. Each of the unicellular, non-glandular hairs contains a crystal of calcium carbonate in the basal portion. They are often referred to as cystolith hairs.

e. Demonstrations of Identification Tests. Attach a cigarette suspected of containing Marihuana to a small test tube with a paper clip and pour 5 ml. of petroleum ether (benzin) into one end so that the liquid flows through and collects in the bottom of the test tube.

   1. Pour one-half of the liquid thus obtained into a small porcelain evaporating dish and allow to evaporate. Add a few drops of 1% alcoholic-potassium hydroxide to the residue. A purplish color, darkening on standing, is produced.
   2. To the remainder of the petroleum ether in the test tube, add 1 ml. of a saturated solution of hydrogen chloride gas in absolute alcohol. Shake and allow to settle; the lower layer should be distinctly pink.

   Record the results of each of the above tests.

f. Examine the newspaper and magazine articles and other literature dealing with the use and misuse of Marihuana. These are on display in the laboratory.

As I approach the concluding part of this paper I should like to discuss briefly the subject of "teaching aids". Among the usual adjuncts that we use are the following:-

1. Field trips to the Medicinal Plant Garden and, at times elsewhere
2. Living materials brought to the laboratory from the Medicinal Plant Garden, etc.

3. Preserved materials
4. Herbarium and other dried specimens
5. Charts, both professional and "home-made"
6. Models
7. Chalkboard drawings and diagrams
8. Bulletin boards in laboratory
9. Reference books, etc.

Still other "aids" that we use to a greater or lesser extent are those named and discussed below.

10. "Special Points":- A number of years ago the late Professor Leslie M. Ohmart and Professor Mitchell J. Stoklosa approached us concerning the possibility of the students receiving certain added points of information in pharmacognosy that would aid them (the students) in certain courses in pharmacy. Of course we were very pleased to cooperate. Dr. VanderWyk and I met with the previously mentioned teachers of pharmacy a considerable number or times for the purpose of bringing the desired material together. Many hours were spent before all of this material was finally completed and in typed form. The information so gathered is presented during lectures when the appropriate drugs are being considered. For the want of a better name we usually refer to this information as "Special Points".

    Students are required to record this information on index cards or, if they prefer, in compact loose-leaf notebooks. The cards or the pages of the notebooks must be arranged alphabetically by drug names, and we recommend cross-indexing of the information. The sets of "Special Points" are checked by us on a number of occasions during the year, usually at examination times.

SPECIAL POINTS

Solanaceous Drugs and Their Derivatives

1. Belladonna Liniment, not official
   a. Is so different from most liniments that it must be used with caution.
   b. Consists mainly of Belladonna Root Fluidextract with 50 Gm. of Camphor dissolved in 800 mls. of the fluidextract and enough of the fluidextract then added to bring the volume up to 1000 mls.
   c. Unless it is applied cautiously there is danger of poisoning because of absorption through the skin.

Solanaceous Drugs and Their Derivatives - continued

2. If Belladonna Fluidextract is prescribed and the exact one not specified (whether of the root or leaf) it is advisable to use Belladonna Leaf Fluidextract, N.F. X.

3. Belladonna Extract, N.F. X
   a. Prepared from the leaf drug.
   b. There are two official forms (included in the same monograph)-
      i. Pilular Belladonna Extract.
      ii. Powdered Belladonna Extract.
   c. Both must have the same alkaloidal content according to the N. F. X.
   d. Specific uses -
      i. Pilular - in ointments and suppositories
      ii. Powdered - in tablets, capsules, and powders.
   e. The powdered extract can be used in place of the pilular in ointments and suppositories, but it is probably advisable to have both available in the store.
   f. If the powdered form is used in ointments and suppositories it can be moistened with a small amount of dilute alcohol. This brings out the green color.
   g. In recent years it has sometimes been difficult to obtain the pilular extract on the market. It is available from S. B. Penick and Company, 100 Church Street, New York 8, New York.
   h. The pilular extract, if stored in collapsible tubes, can be conveniently used.

4. Belladonna Tincture, U. S. P. XV, is sometimes prescribed in capsules with such materials as aspirin. Use an equivalent amount of the extract.
5. The various solanaceous tinctures are rather strongly alcoholic. Watch out for materials being thrown out of solution when these preparations are prescribed with aqueous ingredients of a prescription. SHAKE label may be needed.

6. Atropine Sulfate Solution for use in the eye rarely runs over 2%. (Mention purposes.)
7. Suppositories containing as much as 1/30 grain of Atropine Sulfate per suppository are rather commonly encountered.
8. Atropine Sulfate is used in pediatrics in extremely small doses, sometimes as low as 1/1000 to 1/2000 grain per dose.
9. The pharmacist is sometimes called upon to make tablet triturates of these strengths.

Solanaceous Drugs and Their Derivatives - continued

10. Scopolamine Hydrobromide, U. S. P. XV - also known as Hyoscine HBr
    a. Prescriptions are sometimes received calling for Schlesinger's Solution in rather small volumes.
    b. Formula for this solution -

Scopolamine HBr	0.25 Gm.
Morphine HCl	20.00 Gm.
Ethylmorphine HCl	40.00 Gm.
Dist. water, q.s.	1000.00 ml.

    c. Dosage of the above: - usually 2 or 3 drops.
    d. Keep this formula where it will be available when needed.
    e. It is suggested that you make a collection of formulas some of which are difficult to locate elsewhere when needed.

11. Homatropine Hydrobromide, U. S. P. XV is the hydrobromide of a synthetic relative of Atropine.
12. Action on the eye is not as prolonged as is that of Atropine Sulfate.
13. 1% solution is the strength usually prescribed for use in the eye. 2% solution encountered less commonly.
14. Volumes prescribed usually small.
15. Stramonium Extract, not official, is sometimes prescribed in doses which are several times the average dose for treatment of bronchial asthma. Average dose of this extract is 20 mg. (1/3 grain).

Aspidium Oleoresin, U. S. P.

1. Upon standing this preparation separates into two regions, a granular layer and a more fluid layer. The preparation should be thoroughly mixed before dispensing.
2. It is dispensed in capsules and as an emulsion. Do not use a fixed oil in preparing the emulsion. Treat as a volatile oil emulsion type.
3. Preparations containing Aspidium Oleoresin should bear this warning statement on the label:
"Warning. Avoid taking castor oil or other oil cathartics or fats while this drug is being administered".
The label should also bear directions for the administration of a saline cathartic.

Aspidium Oleoresin, U. S. P. continued

*4. Since it is the most commonly used drug for the elimination of tape worms, you should know about its administration in case a physician seeks your advice. Be sure to know this schedule.
   a. A fat-free diet is employed for 48 hours prior to start of therapy.
   b. A liquid diet is employed for 24 hours prior to use of drug.
   c. The evening before a 15-30 Gm. dose of Na_2SO_4 is used to empty the bowel.
   d. The following morning 2 doses of 2.5 Gm. each of the Oleoresin are given 1 hour apart.
   e. Two hours after the last dose a saline purgative is administered.
   f. Two hours later a soap suds enema is given to remove the worm head.

5. Precautions: A course of therapy must not be repeated sooner than 7-10 days.

   The presence of fats in the intestinal tract may result in the absorption of the Oleoresin and in severe poisoning. Common symptoms are : -

headache	diarrhea
cold sweat	mental disturbances
vomiting	convulsions followed by respiratory failure

   The drug should not be used in the treatment of debilitated patients, or during pregnancy, or in the presence of cardiac, liver, or kidney diseases, nor in cases of ulcerated lesions of the gastro-intestinal tract.

6. Total dose for adults is 5 Gm. For children 0.5 Gm. per year of age up to a maximum dose of 5 Gm.

Poison Ivy Dermatitis - (This information already included under appropriate section.)

Copaiba Balsam

1. Be familiar with solubilities - a. Almost completely soluble in absolute alcohol.
   b. Partially soluble in alcohol.
   c. Insoluble in water.

*Note- This schedule through the courtesy of William E. Hassan, Jr., Ph.D., Associate Director of the Peter Bent Brigham Hospital, Boston.

Copaiba Balsam - continued

2. Sometimes prescribed in an aqueous vehicle. Must be emulsified. Treat as a volatile oil in preparations.

Thymol, N. F. X.

1. This material has a low melting point; somewhere between 48° and 51°.
2. But when melted it remains liquid at a considerably lower temperature.
3. Because of this property it is often melted and then incorporated into a preparation in a liquid state. Remember this.
4. Because Thymol can be powdered only with difficulty, melting and incorporating is to be preferred over powdering and mixing.

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11. Prescription specialties and other preparations:- Over the years we have built up our own departmental collection of prescription specialties and related preparations along with appropriate manufacturers' literature and other printed matter. The collection of specialties used in the teaching of our courses includes only those preparations containing materials of biological origin. Of course other ingredients may also be present. Pharmaceutical manufacturers have been very cooperative in helping us to build up our collection and in helping us to keep it up-to-date. You can well imagine that the number of products of certain drugs or groups of drugs is rather large. Manufacturers' literature is filed by drug name and is made available to the students along with the products as they are displayed in the laboratory. Students make use of specially ruled sheets for recording information about various products.

12. Displays:- During as much of the time as possible through the school year we have displays set up in the pharmacognosy laboratory. Usually some of these displays consist of materials related to the subject matter being considered at the time. Prescription specialties and literature are used extensively for this purpose. However, displays are certainly not restricted to these items.

Labeled jars of crude drugs as well as bottles of volatile oils and related materials are stored permanently

12. Displays:- continued
on open shelves in the laboratory, and are always available to the students as are all other displays. Other educational materials are also displayed.

13. Mimeographed sheets:- On some occasions we find it helpful to furnish information in mimeographed form to the students. Of course such a practice conserves lecture and laboratory time, and the students all have the same information. We use this method of getting information to members of the class whenever it seems advisable.

14. Opaque projector:- The opaque projector is utilized to a limited extent, especially for making use of book illustrations and other pictures. Actual packages of commercial products and even specimens of crude drugs can be projected with this instrument.

15. Films:- The value of motion picture films as teaching aids is too well known to require discussion before this group. I shall state simply that we do use films from time to time. The most recent one used was the Fritzsche Brothers' film by Dr. Ernest Guenther entitled, "Essential Oils of Africa". This is a 27-minute film in sound and color. We showed this excellent film to our third-year class just last April.

16. Slides and film strips:- Colored slides and film strips are used in our teaching somewhat more often than are films. Most of the 2 x 2 slides in our modest collection are ones that we have taken, although we have purchased a few and some have been given to us. You are all aware of the usefulness of slides as teaching aids, and I'm sure that nothing else need be said in their behalf.

AN INDIVIDUAL APPROACH TO THE PRESENTATION OF THE ESSENTIAL TOPICS

II. Based on Cellular Contents and Activity

Jack L. Beal

I feel now somewhat like I did after trying to fix my television set one day this past Spring. We had a television set which began to give a bad picture. It was a set that I was going to sell within a month. Rather than spend money for a service charge, I decided to test some of the T.V. tubes myself. So I took most of the easily accessible tubes to a do-it-yourself tube tester and ended up by replacing four tubes totaling $12.75. After the tubes were put back into the set, to my surprise, the set became worse than ever, and it began to smoke, and an acrid odor developed. So I hurriedly pulled the plug and called a T.V. serviceman and truthfully told him my story. When he checked the set he found that the trouble was in a metal enclosed tube that I had failed to test. This tube was shorting out and had caused the trouble. In addition one of the tubes I had bought was not as good as it should be. The serviceman charged me an additional $11.50 and admonished me as he went out the door with the statement, "You don't touch the T.V. set and I won't try to teach nobody nothing."

As I stand before this distinguished group I see the faces of many people whom I respect very much and who have impressed me by their writings and their reputation as educators and men of research. So I feel now somewhat like the T.V. serviceman--- I don't believe I am going to teach this group anything. However, if you all will contribute, as I know you are capable of doing, to the discussion that follows, then perhaps something worthwhile will be gained from the effort.

As I see it, the major problem in teaching pharmacognosy today is not the classification we follow in presenting the material. If I were to speak at great length on why the chemical classification should be used and gave a convincing argument, I am sure that it would not cause those of you with a strong botanical background to change from a botanical classification. If I were to reverse the situation and gave a good argument for a botanical classification, I am equally convinced that it would not budge those of you with a strong chemical

background to change your method of classification. The choice of classification you use is, in most cases, for good reason. Often it is the method by which you feel the most natural and the one with which you can do the best job that is chosen.

Dr. Gunnar Gjerstad wrote a thought-provoking article in the past January issue of the American Journal of Pharmacy in which he pointed out the diversity of course content in pharmacognosy today. He stated "This diversity of course content today, in my opinion, constitutes the greatest weakness towards the justification for teaching pharmacognosy." He went on to suggest that a core syllabus ought to be agreed upon by a majority vote. Idealistically this suggestion is good and seems reasonable. Realistically it would be most difficult to work out. Course content varies from school to school usually for good reason. Deans seldom get to start from scratch in choosing their personnel. A Dean can make some changes and he can bring in some new men, but he is still limited somewhat. So assignments of courses to be taught are made with his utmost ability utilizing the personnel he has on his faculty, thus varied backgrounds of pharmacognosy teachers result. In addition, a point which should not be overlooked is that this country is large and is made up of people of many different cultural backgrounds and schools of thought accentuated by our philosophy of free speech and free thinking. This nurtures different viewpoints or ways of thinking of things, and as a result we have many diverse opinions of course content in all courses in pharmacy. During a portion of my graduate student days I was an instructor at the University of Kansas and assisted Dean J. Allen Reese in teaching pharmacognosy. At that school all drugs of biological origin were taken up definitely in the pharmacognosy courses. At Ohio State University, where I now teach, the drugs of endocrine origin are taught in a course called Glandular Products. Drugs of bacteriological origin are taken up in a course called Biologicals. Although these two courses, Glandular Products and Biologicals, are within the area of pharmacognosy they are being well handled by members of our pharmacology department.

At one time I thought that pharmacognosy could only be taught by a person with a pharmacognosy major. Some still think along this line. I no longer believe this necessarily to be true. From my own experience I know of some schools where the respective teachers of pharmacognosy are not persons with a pharmacognosy major, and I know for a fact that their courses in pharmacognosy don't have to take a back seat to anyone's. I hope, before I am through, that I will have

clearly explained why this is so, for herein lies the major text of my talk.

Most of you have heard sometime or other some disparaging remarks from teachers in other fields of pharmacy such as "Pharmacognosy is sick!" Pharmacognosy is no more sick than their field of pharmacy. If their field of pharmacy is sick, as well as pharmacognosy, then it is not because of their methods of classification of drugs for teaching purposes, it is not because of the diverse course content from school to school, it is not necessarily due to the fact some people are teaching a course which was not their major in their graduate work. The real reason they are sick, if this is so, is because we who teach the courses are to blame. If pharmacognosy is in low esteem, it is because we who teach it have allowed it to be placed there and there is no excuse for it.

I have had a wonderful experience this past year on a Fellowship. I sat in a number of classes and I observed things much differently than ever before. It is not too difficult to determine whether a person is a good teacher or not. The students soon know, believe me. I will long remember one of the courses I audited. It was taught by a man loaded down with administrative duties as well as being the advisor of a good many graduate students. Yet this man presented one of the most well-organized and stimulating courses I have ever witnessed. How did he do it? It was evident that he loved teaching, and it was evident that he felt compelled to give a course that was up to date in every detail and one that was meaningful. I am told, and I well believe it, that this professor shuts himself in his office one hour before his class and goes over the material he is to present for the day. This perhaps is nothing to some of you. But how about it? How many, after several years of giving a course, prepare themselves for fifteen minutes before giving a lecture? How many have revised their courses in recent years to keep up with new information? How many keep up with the literature so that they even know what is new information? In short, how many really make an all-out effort to be a good teacher of pharmacognosy? If this hits you where it hurts, don't be angry with me and wonder what right this upstart has in asking these questions, because I stand before you as a sinner <u>too</u>. I am going back to Ohio State resolved to make a greater effort to be a better teacher, and my courses are going to have to undergo revision. I am conceited enough to think, though, that if this is true of me then it is also true of some of you.

This is why I state that a man does not necessarily need a pharmacognosy major to teach a good course in pharmacognosy. When I made that statement I had in mind the teachers I know who are so dedicated to teaching that their efforts shine through and their pharmacognosy courses are good ones.

However, if you are not a pharmacognosy major and are teaching the course because it was assigned to you, and you feel no compulsion to make a good effort, then you are not doing a service to the student, your school, pharmacy nor pharmacognosy. If you are a pharmacognosy major, and you likewise have not enough enthusiasm and love of your profession to do a creditable job of teaching, then the crime is even worse. I suggest that we all honestly evaluate ourselves and adjust accordingly.

In spite of the comments made yesterday in regard to our present textbooks of pharmacognosy, it is my considered opinion that we do have some good textbooks in this field. As I see it a textbook is to serve as guide and an aid and it should not be expected to do all of the work for a teacher. The literature on new discoveries and developments is abundant, teaching aids are getting more plentiful and some are very good. There is no reason why we cannot become more dedicated and stimulating teachers of pharmacognosy, and, as we do, the student, the school, pharmacy and pharmacognosy will profit.

I have been assigned the topic "An Individual Approach to the Presentation of The Essential Topics Based on Cellular Contents and Activity." I have been told that one of the reasons I was assigned this topic was that it is known I use a chemical classification, as many of you do. I have already made the comment that I do not feel the classification system for study of drugs is our major problem. This does not mean, though, that I think it does not deserve due consideration of a teacher in pharmacognosy. In choosing the classification one must consider many things such as your background, a method that allows one to cover a great deal of material without decreasing the quality of the course, and probably one of the most important, a method that will aid one in placing the emphasis of course content where it rightfully belongs.

Medical Science has progressed quite rapidly in recent years which has brought about a wealth of new information on old drugs and the discovery of new drugs. We find that the practice of pharmacy is changing as a result of many factors. Just how pharmacy is going to resolve or transform no one

really knows. There have been some suppositions as to what pharmacy will be in the future and some seem sound to me. You know of them, as well as I. For one thing, if pharmacy is to progress as we all want it to, we teachers have a great responsibility in helping it along, for it will be the products of our efforts which will be making this change. Claude Bernard once said "In science the important thing is to modify and change one's ideas as science advances." It is important that we keep this in mind. We can't teach pharmacognosy as it was taught 15 years ago nor ten nor five. We must teach pharmacognosy for today and for what we think and hope tomorrow will be. The goal for the future of pharmacy in all of these suppositions is high and only a student who has a good sound foundation of knowledge for today can go along being a credit for pharmacy now and in the future. A good many believe as I that a retail pharmacist today does not need to be able to identify an Atropa belladonna or Digitalis purpurea plant. He really doesn't even have to know anything about their habits of growth. But he had certainly better know all about the constituents of importance that they contain, and how to make an acceptable drug form from them if the need occurs. To be sure I utilize our medicinal plant garden, the students see some drug plants in the garden, and I discuss some drugs right there on the spot, but the emphasis in my course is on the constituents in these plants, for it is because of the constituents that they are called drug plants rather than weeds or plants of the flower garden. In some cases it is not only the constituents responsible for its pharmaceutical or therapeutic use that is important. For sometimes other constituents present in the drug modify the action or bring about incompatibilities and these constituents also must be mentioned.

According to the newly revised curriculum at Ohio State, we give 18 quarter hours of required courses in the area of pharmacognosy. Of the 18 quarter hours, six hours constitute the Glandular Products and Biological Products courses, to which I have already referred. The remaining twelve hours are divided into a nine hour general pharmacognosy course and a three hour lecture-laboratory course. The nine hour course is given in the first two quarters as a five hour and a four hour presentation. They consist of four lectures a week with the five hour quarter course having, in addition, one laboratory each week of three hours length. My next remarks will concern the nine hour course.

After two weeks of introductory material, historical background and general information the course material is

devoted in imparting basic knowledge of the drugs of plant and some animal origin and their constituents which are useful for their pharmaceutical and/or therapeutic use. The intent is to provide a background which makes possible an intelligent handling and understanding of pharmaceuticals which contain these drugs. The method of classification that I use is not original with me. It is essentially the same as the chemical or biochemical system suggested in the book "The Pharmaceutical Curriculum" by Lloyd E. Blauch and George L. Webster. It is modified to the extent that the alkaloidal bearing drugs and the volatile oil bearing drugs are subdivided according to the plant family to which the parent drug plant belongs. This is done for several reasons which I will not defend unless requested to do so in the discussion period. I make no boast that my procedure is better than any of yours. Some of you, I am certain, use the same classification. Much can be said in favor of other classifications such as, for example, the therapeutic-physiological which likewise tends to place emphasis on the active constituent and the biogenetic which is very challenging and fascinating and which I feel will do much in placing pharmacognosy on a higher plane.

I will not go into detail concerning the classification I use since it is not original with me and follows so closely a well-publicized system. Briefly the drug plants are taken up according to the general chemical classification of the main constituent. Thus we have those drugs that are either carbohydrates or are drug plants important because of the carbohydrates they contain, the same is true for glycosides, tannins, lipids, alkaloids, antibiotics, volatile oils, etc. In some cases the general heading can be further subdivided. For example, carbohydrates could be subdivided by several different methods, one of which would be dividing them into sugars, polysaccharides and derived carbohydrates. Another example could be sub-dividing lipids into fixed oils, fats, waxes and phospholipids.

In using this method of classification it is essential that the student has a background of organic chemistry, otherwise it would be too difficult for him to grasp a true meaning of the material. Even though the student has a background of organic chemistry it is essential that there be a general discussion of the type constituent before the individual drugs which contain the type constituent are discussed. It is essential because, while organic chemistry gives the student a good foundation of basic material, he still needs to have explained to him in greater detail the meaning, nomenclature and properties of the general heading such as glycosides, alkaloids, etc.

For my course the plan of study includes a general discussion of the type constituents followed by a study of drugs which contain the constituents. Every official drug of plant origin is at least touched upon, but the attention devoted to any given drug will vary as to the pharmaceutical or therapeutic importance of the drug at the present time. The lecture material places emphasis on the important constituents of the drug such as their isolation, physical and chemical properties, incompatibilities, storage and in some cases information on their biosynthesis. Additional material sometimes emphasized is the cultivation, production and commerce of the drug. In a few cases a historical background of the drug is given. At the suggestion of Dean Lloyd Parks and Dr. Hampton Hoch I have made up study sheets for the students that have proved helpful. It serves several purposes such as serving as a guide to the students as to what is expected of them; forcing the student to use the books in the library, thereby acquainting him with reference sources; and facilitating class discussion of the more major points of the assignment.

The laboratory for this course is in the process of revision and is subject to the approval of our Dean and his faculty. It is essentially a laboratory concerned with extraction. It will be proposed that a portion be devoted to the methods used in making drug forms from plant material by extraction procedures such as tinctures, fluidextracts and extracts; a portion will be devoted to the isolation of active constituents of plant drugs as a means of emphasizing the physical and chemical properties of the constituents; another portion of the time will be devoted to an introduction to methods used to separate constituents that have similar properties. These methods will include column and paper chromatography and a demonstration of paper electrophoresis.

To complete the picture of undergraduate pharmacognosy in terms of required courses at our college I will briefly describe the lecture-laboratory course. It consists per week of three lecture-laboratory periods of two hours each and is open for graduate credit. It may be described as a course embodying the principles of the microscope and the application of microchemical and specialized techniques in the detection, separation and identification of drugs. The course outline includes a discussion of the basic principles of the microscope. The student is taught how to standardize the microscope, and then an assignment is given to illustrate how the microscope may be used to measure a microscopic object, such as the determination of particle size. The student is introduced to how the micro-

scope may be used to determine the refractive index of a crystal, and a laboratory experiment is assigned to illustrate the principle. A lecture is given on quantitative analysis using the microscope with discussion of such things as the Wallis lycopodium method and the quantitative work of Heber Youngken, Jr. and Robarts Proper. Lecture and assignments are made concerning microchemical techniques such as for the determination of solubility, micro-sublimation, micro-extraction, micro-filtration, and micro-crystallization. The student is given some exercises in methods of identifying drugs of toxicological or legal importance from tablet and capsule forms (such as alkaloids and barbiturates). This is followed with a series of micro-chemical tests for constituents within the plant cell. And finally the student is introduced to how histological characteristics together with micro-chemical tests may be utilized for the identification of a specific powdered plant drug.

This course can be followed up with an elective which is also open for graduate credit in which the student is taught how to use the polarizing microscope to determine the optical properties of crystalline substances, how to take pictures through a microscope and how to use various other accessories to the microscope that might be research aids or useful for teaching purposes.

This, in general, is how pharmacognosy is presented at our College. No doubt there are many of you sitting there somewhat perplexed and saying to yourself "He certainly did not present much of anything specific. Just what does he really give in his general pharmacognosy course?" You are correct. I was not very specific. I was general in my information purposely. Most likely you cannot give at your school what I give at mine and I can't give what you give. This was in part what Dr. Gjerstad was objecting--- the diversity of the material at our schools. What must one do? The answer, as I see it, is to meet with your fellow faculty members and determine what you must cover and then make an effort to correlate as much as possible your material with that of your fellow faculty members. There is no doubt about it, to be a good teacher it takes a great deal of effort; and if we don't make the effort, then, believe me, we will not be good teachers. Then we must follow through by being enthusiastic and sincere with our presentation, for if we are not, then we certainly cannot expect the students to be. We must be positive in our manner and outlook. We cannot be apologetic about teaching pharmacognosy as some have been. We must be proud of being

able to represent pharmacognosy and exert every effort to make ourselves worthy of this responsibility by modifying and changing our concepts as medical science progresses. Through our enthusiasm and dedication it is to be hoped that more students may be stimulated into doing graduate work in the area of pharmacognosy.

The Conference of Teachers and the American Foundation for Pharmaceutical Education are to be congratulated for sponsoring these seminars whereby we can meet together and exchange information and ideas. As I see it, we can only talk in generalities, but out of it all we are bound to learn many worthwhile things, gain some ideas for better teaching methods and, in addition, take back with us to our respective schools a feeling of inspiration to be more dedicated in becoming better teachers of pharmacognosy.

LABORATORY PRESENTATION OF THE ESSENTIAL TOPICS IN PHARMACOGNOSY

Stephen K. Sim

The laboratory presentation of the essential topics in pharmacognosy is governed by (a) what are considered as the essential aspects within the scope of pharmacognosy in the study of drug substances from biological sources, (b) which among these aspects are to be given greater or less emphasis in a basic pharmacognosy course, and (c) what do we wish to see the student learn from such laboratory work, or, in short, the objectives.

The first of these factors has been examined and discussed in various text-books and in other papers in this seminar. There seems to be general agreement regarding the aspects with which pharmacognosy is concerned, and these include the collection, identification, and preparation of biological materials of medicinal and pharmaceutical significance, and the separation, extraction, evaluation, and formation of their constituents. The topics for laboratory presentation must reflect, illustrate, and correlate the topics in these aspects discussed in the lecture courses.

The emphasis given to particular aspects of the subject matter of pharmacognosy has been undergoing a fairly definite shift in direction in the last fifteen years or so. Greater emphasis is now given to the study of the constituents in their biological context than was formerly done. The reasons for this shift of emphasis have been fully discussed by pharmaceutical educators and by pharmacognosists such as in the Blauch and Webster Report on the Pharmaceutical Curriculum (1952), in the previous Teachers Seminar on Pharmacognosy in 1953, and in the present Seminar. The variations in the emphasis on the constituents and in the proportions of laboratory exercises given to the study of the constituents shown in the different pharmacognosy laboratory manuals available at present may be seen as manifestations of the different degrees to which these authors have responded to this new trend.

In presenting laboratory exercises, two primary objectives are: 1. to give the student a first-hand knowledge and truly meaningful appreciation and understanding of the terms,

descriptions, and discussions in the literature pertaining to drug substances from biological materials, and 2. to familiarize the student with the more important basic techniques which are frequently used in the preparation and study of these drug substances. It is no exaggeration to say that a good many descriptions and discussions in the literature which a pharmacist has to read in connection with his professional work would have little or no meaning to him unless he has had some laboratory experience dealing with such descriptions and discussions.

The following proposal is based on the acceptance of the trend for increased emphasis on the study of the constituents and on the objectives mentioned above.

On such a basis, the laboratory exercises to be carried out in a basic pharmacognosy course may be grouped into four categories: 1. macroscopic examinations, 2. microscopic examinations, 3. study of constituents, and 4. biosynthetic processes.

1. Macroscopic Examinations. - As pharmacognosy deals with biological organisms and their parts as sources of drug substances, the student should be given the opportunity to acquaint himself with these raw materials. As rather few of these drug substances are now used in the crude drug or raw material forms, a detailed study of these need not be attempted in a basic course. A suitably selected number of representative medicinal plants as whole live plants, as herbarium specimens, and as the dried parts such as roots, leaves, barks, etc., may be briefly examined in each laboratory period in conjunction with what is currently being discussed in the lectures. Only a small portion of the laboratory period need be allotted to this.

2. Microscopic Examinations. - While only a small number of plant drugs are now used in pharmacy and medicine in the forms of roots, leaves, etc., the identity of the correct root, leaf, etc., from the correct plant species is of obvious importance. This is so from the point of view of safeguarding against adulteration and from the point of view of obtaining specific constituents from particular plant species. For instance, different species of Digitalis may contain different glycosides and in different quantities. The same may also be said about the alkaloids in different species of Rauwolfia. Therefore an exposure of the student to the techniques involved and the tissue elements to be looked for in the identifi-

cation of powdered drugs and sections of plant parts by microscopy is desirable. For this purpose, I think it would be convenient as well as instructive to examine a few important examples of the various plant organs, i.e., root, leaf, bark, seed, etc. It should be sufficient to aim at familiarizing the student with the different tissue elements (such as trachea, fibers, trichomes, etc.) and the inclusions (such as calcium oxalate crystals, starch granules, etc.) in these plant organs in transverse and longitudinal sections and in powdered samples. The student will examine how these elements may differ from one drug plant to another and compare these features in a given sample with descriptions given in reference books or identification keys. Such exercises would also enable the student better to understand similar descriptions of these drug plants in the literature. In a basic course, I think it would not be necessary to require the student to memorize these microscopic features for the different drug plants. A good deal of the laboratory time would then be left for exercises concerned with the constituents. Perhaps two well chosen examples for each plant organ from well known drug plants may be sufficient for these exercises in microscopy.

3. Study of Constituents. - If one agrees with and accepts the recent trend for increasing emphasis on the constituents in pharmacognosy, then it is only logical that the laboratory presentation of the subject should also reflect this trend. It seems to me that in a good many, perhaps most, colleges of pharmacy, the pharmacognosy laboratory exercises have lagged behind the lecture courses in this increase of emphasis on the study of the constituents. I would suggest that the laboratory exercises and experiments dealing with the constituents should occupy a major portion of the total laboratory time.

Constituents which are related to one another in their chemical nature often lend themselves to similar or closely related chemical tests and extraction and isolation procedures. Therefore the laboratory exercises dealing with the study of the constituents may be best organized according to chemical groups such as carbohydrates and their derivatives, glycosides, alkaloids, fixed oils, volatile oils, etc. Perhaps one to three laboratory periods may be devoted to exercises or experiments involving substances belonging to each of these groups. These exercises may include simple qualitative tests, histochemical reactions and microscopic examination of crystals, extraction and possibly certain preliminary steps of isolation and purification of some of these constituents from plant

materials. One or two quantitative estimations or assays of the constituents in these extracts by chemical or physical assay methods may also be included.

Depending on the number of students and of instructors, and on the availability of equipments and other facilities, the nature and scale of these laboratory exercises will necessarily vary from one college to another. Some examples of laboratory exercises along these lines are as follows:

For the carbohydrates and their derivatives, the student would carry out microscopic examination of various starch granules, various simple tests for starch, sugars, cellulose, and gums, and preparation of starch from maize or potato.

As examples of exercises involving plant acids and their salts, microscopic examination of calcium oxalate crystals from different plant drugs, extraction and text of aconitic acid from Aconite, and separation of citric acid from Citrus fruit or from cultures of Aspergillus molds may be carried out.

For the glycosides, extraction and estimation of glycosides from Digitalis or other glycoside-containing plants, simple chemical tests for the cardiotonic glycosides and the anthraquinone glycosides may be performed. Preparation of emulsin from almonds and tests of emulsin's actions on the glycoside amygdalin may also be included.

For the alkaloids, the student would acquaint himself with the various simple color reactions and crystal formation of the more important alkaloids with the use of several of the common alkaloidal reagents. Extraction and estimation of the total alkaloids from a Solanaceous plant or other alkaloid-containing plant material may be carried out with the use of Soxhlet extractors and other extraction techniques.

A number of simple tests for various fixed oils and volatile oils, and preparation of volatile oil from selected plant materials by steam distillation, extraction and tests of vitamin B_{12} from liver extracts or from Streptomyces cultures, and color or biological tests on some of the antibiotics are examples of other possible exercises.

4. Biosynthetic Processes. - As part of the study on constituents, the biosynthesis of the various constituents is becoming an important interest in pharmacognosy. It is interesting

to note that a recent edition of a well-known pharmacology text-book has pointed out that the present-day pharmacognosist is very much concerned with the biosynthesis of drug substances by plants, fungi, and other biological organisms. Apart from the obvious academic significance, it is pertinent to recall that biosynthesis has some important practical implications as well, as witness the production of antibiotics, the possible use of biosynthetic steps to complement the chemical synthesis of certain steroid compounds, the production of certain organic acids by molds, and formation of dextran by bacteria. Therefore it would be of interest to introduce the student to a few glimpses of these aspects by using as laboratory exercises a few selected biochemical reactions which are directly or indirectly involved in the biosynthesis of drug constituents from biological materials. It also should be possible to include one or two laboratory exercises in which microbiological organisms are cultured and subsequently extracted for specific constituents. The growth of suitable Aspergillus species for citric acid formation, and of Streptomyces species for vitamin B_{12} have already been mentioned. Some antibiotic-producing organisms may also be used.

Organization of Laboratory Exercises. - It will be possible, indeed desirable, to dove-tail certain laboratory exercises of the different types described above. That is to say, during a given laboratory period, macroscopic examination of appropriate plant specimens, microscopic examination of sections and powders of plant parts, and a part or the whole of an exercise or experiment involving chemical tests or extraction of constituents may be carried out. Microscopic work may be carried out, for instance, when the student is waiting for an extract or solution to evaporate or when a standing period is required in the procedure. Also, some of the exercises as indicated above would be more suitably performed by students in groups of two or more, while others would be better carried out individually.

One would be able to incorporate all the types of laboratory exercises and in the proportion and to the extent suggested here in a total of perhaps twenty to twenty-four laboratory periods of two or three hours each. In practice, this would mean then one laboratory period per week for two quarter terms or two semester terms excluding examination periods.

To my knowledge, a number of colleges of pharmacy in the United States and Canada have been for several years past

presenting their pharmacognosy laboratory courses in forms and organization similar to what I have indicated here. On the other hand, a good many others have continued to place greater emphasis on microscopy. Most of the exercises concerned with the constituents as suggested here have also been carried out in several colleges with varying degrees of success. These exercises suggested here are mostly based on my own experience but are not at all meant to be considered as the only possible ones. I think there is ample room for experimentation. The direction in which the laboratory courses in pharmacognosy must take will inevitably depend upon the extent to which the trend of increasing emphasis on the study of the constituents is accepted and implemented for the scope and subject matter of undergraduate pharmacognosy.

DISCUSSION

Question: Are laboratory assignments of a given period a separate project or are they integrated into the total program of the course? One segment on constituents themselves; another segment on biosynthetic pathways?

Sim: I attempt to outline the total program and then have separate phases carried on in overlapping procedure. Short-time operations can be done while longer duration projects are in progress. The total time consumed should cover the many phases of the work.

Tyler: The writer of a Laboratory Manual must be a prognosticator. With the deemphasis of certain phases and with new emphasis--would you continue experimentation of the microscopy of powdered drugs, say five years from now?

Sim: Yes. The pharmacist must be depended upon for identification of crude drugs. The literature makes references to them. Clarification of the differences between different species of a genus must be made and it is the function of the pharmacognosist to make these distinctions.

Koffler: Do you have students working individually or as groups in the operation of the laboratory work?

Sim: This varies with the school, the amount of equipment, and the number of students. We have two sections and

students work in pairs on all of the experiments.

Parks: Microscopy has many important applications in addition to the use in identifying crude drugs. This is the area of the pharmacy curriculum where microscopic work is done. Pharmacognosy can make a very desirable contribution to the total education in pharmacy by serving these areas of microscopic study.

Redman: Microscopic and macroscopic descriptions are included in the USP and NF. If our students aren't able to intelligently read the official compendia, who in heaven's name is supposed to read and use them?

Pokorny: In reference to extraction by the soxhlet--isn't a good deal of the extraction possible by micromethods and can't this be used more easily in the laboratory?

Sim: I have used 2-3 soxhlet extractions and a considerable number of micro extractions throughout the total year's work. A number of biochemical reactions can be carried on just as satisfactorily in micro quantities.

Ramstad: We emphasize groups, e.g., antibiotics, serums, hormones, etc. What do you think of the feasibility of including experiments on these groups specifically?

Sim: I think wherever possible they should be included in the experimental phase of the course. Thus far I haven't included laboratory exercises on serums or vaccines.

Youngken Jr.: Several nice experiments on enzyme specificity are applicable to the work (protein reactions involving enzymes in sera). An up to date pharmacognosy laboratory might well have a Warburg apparatus and interest in the phases that are possible with such instrumentation might well be included.

Mc Connell: Biologicals might be difficult. Antibody-antigen reactions might well be used as an example of such specificity.

Gjerstad: Which type of examinations are you using with your work?

Sim: I consider the laboratory a part of the full course. Lab exams are given along with lecture exams. In the

laboratory I use a system of unknowns and identification samples to be worked out during the laboratory assignment. Crystallization and color tests are included. These do not include powdered drugs as such, but this phase of work is carried on at the same time.

RECENT ADVANCES IN THE BIOLOGICAL SCIENCES OF INTEREST TO PHARMACOGNOSY

Frank A. Crane

The responsibility of recognizing and assessing advances in any field is a great one. In a hybrid science such as Pharmacognosy the problems are even greater for the line between items of interest and nonrelevant areas is often vague or non-recognizable, and the magnitude of personal interest is as great as there are workers in the field. For these reasons I have chosen to consider publications produced within this decade, and those published as individual works or reported in the American Journal of Botany, Plant Physiology, Annual Reviews of Plant Physiology and the Journal of Experimental Botany. I realize that there are other excellent publications that might and should be included but the physical boundary of our time limit precludes further branching out. I have not included references of the regular Pharmaceutical Journals assuming that you are already fully aware of these articles and the work they represent.

1. I would refer first to work reported on plants commonly thought of as drug plants or sources of crude drugs.

The composite work on Rauwolfia by Woodson, Youngken, Schlittler and Schneider is an excellent compilation of pertinent information about this plant and its alkaloids.

The Proceedings of the Symposium on Rauwolfia held at Calcutta in October, 1955 lists about 30 articles the majority of which are of direct interest to our discipline. Piringer, Downs and Borthwick found Rauwolfia reacting to photoperiod as a long-day plant where branching was concerned but they were not able to induce flowering during 39 week experiments under any conditions.

The article on Cinchona alkaloids indicated that increased light was directly related to increased nitrogen supply in the production of growth and alkaloids. Forest shading was a major problem in their work.

The review article by Mothes critically analyzed abundant references on formation of alkaloids in root and shoot, translocation and chemical transformation of alkaloids; the genetics

and taxonomy of alkaloid bearing plants, and a good summary of the role of alkaloids in and out of the plant.

The series of articles on Nicotiana extends the information on the relationship of morphological structure and site of synthesis of alkaloids. The production of an actively growing tissue culture of Solanum has led to new knowledge on the rate of synthesis of its alkaloids.

Testing the effect of essential oils on stomatal behavior appears unusual and interesting though one wonders about the motivation and application of the work.

The other papers of the first list are of specialized interest and will be considered if there is time after discussion of some other sections.

The Botanical Society of America celebrated the fiftieth anniversary of its founding in 1957 and observed the milestone by publishing invited papers on selected topics, a few of which were included in monthly issues throughout the year. Several of these were excellent and merit our attention.

H. W. Youngken, Jr. presented "Botany and Medicine" in a challenging modern style. Harry Fuller of the University of Illinois wrote on "The Odor of Botany", taking his title from the derogatory comment of many college and university students. His solutions to the problem are well worth the consideration of all the Pharmacgonosists. Donald C. Peattie attacks the same problem in a very different style.

Some of the articles fall prey to the general tendency to revert to the whimsical in retrospect, but the general tenor is to challenge all of us to accomplishment in the second half of the century. The role of Botanical Gardens in the competition of our times is of real interest to the pharmacognosist and we have yet to see much of the outcome of this problem.

2. and 3. The use of radioactive isotopes, which offer possibility of detection of a particular ion in minute quantities has made it possible to furnish radioactive carbon dioxide to plants and after a suitable growth period, harvest, separate plant parts, and by exhaustive extraction and separation detect the various compounds present. For example, by this method Scully reported four flavonoids in tobacco leaves in addition to the rutin, isoquercitrin and quercitin already known.

A variety of compounds have been unearthed by this method of uniformly labeled compounds grown for a long period of time with radioactive CO_2. A number of radioactive alkaloids have been prepared by Geiling et al, e.g., colchicine, nicotine and morphine. Digitoxin was prepared from air dried leaves of Digitalis purpurea after exposure of 4-6 weeks of $C^{14}O_2$.

Addition of a single compound bearing C^{14} and later compounds that have C^{14} located in a particular position - to a plant part or homogenate, followed after very short to longer periods by critical killing of tissue and extraction, have been useful in elucidating cyclical relationships among the compounds involved in many processes. An excellent example of this technique is the work reported by Basham, Calvin et.al. at the University of California on The Path of Carbon in Photosynthesis. For convenience they made use of the unicellular algae Chlorella and Scenedesmus--exposed these to C^{14} as bicarbonate in nutrient solution for extremely short periods of illumination, then extracted, chromatographed and produced radioautographs of the chromatograms. A large number of radioactive compounds were present even after seconds or less of exposure to the CO_2 in the light. In addition, specific compounds were introduced to the algae via the nutrient solutions and under the control of particular enzymes, concentration changes of various compounds within the algal cells led to the construction of their scheme for the path of carbon in photosynthesis. CO_2 is accepted by ribulose 1-5 diphosphate to produce two molecules of 3-phosphoglyceraldehyde; thus around the cycle to the further synthesis of sucrose, various intermediates for the synthesis of a number of organic molecules, and the resynthesis of some ribulose 1,5 diphosphate to keep the cycle running. The functioning of this cycle has been proved in a number of higher plants as well as the green algae where it was first shown.

This method of approach to the study of enzymatically regulated reactions involving specific enzymes has been effective in determining compounds in the glycolytic degredation of starch to pyruvic acid and the further breakdown of this compound to CO_2 via a series of nine or more steps with a number of small energy releases along the way. The idea that Photosynthesis is the exact reverse of respiration as is often presented to elementary students by the simple chemical equation involving hexose, oxygen and carbon dioxide, is shown to be untrue, though a few cyclical steps do appear to involve the same cycles.

Radioactive ions have been used to show

(a) mechanisms of absorption of inorganic ions and other molecules at rapid rates through the pectic surfaces of leaf cells or even the bark of tree trunks, by an exchange mechanism.

(b) translocation of absorbed growth regulators across mesophyll to phloem and movement with elaborated organic materials. Transfer across a lipoidal barrier seems to be involved.

(c) penetration of fungicides and insecticides into host plants and the spores of the fungi. Possibility of practical uses of systemic insecticides and fungicides have thus been investigated.

(d) The mechanism of translocation of solutes through woody plants and particularly across root and stem grafts are clarified. Control measures have been and can be devised based on the presence or absence of natural grafts.

(e) Even the path of a boring insect within a plant and the total distribution of such insects as mosquitoes have been traced by using radioactive elements and counters. The possibilities for such a diagnostic tool appears almost limitless.

4. The separation, isolation and purification of enzymes has made it possible to introduce such purified preparations under various conditions to selected tissues and evaluate the total enzyme system, and the various references of McElroy's review article on "Mechanism of Action of Micronutrient Elements in Enzyme Systems." Where these enzymes are involved in a major pathway, e.g., the carboxylating and glycolytic enzymes, great advances have been made. Where less in known about the function and occurrence of the enzyme or system, the line of attack has been to extract a tissue, treat the homogenate with a particular reagent that is quantitatively colorimetric upon reaction or one that may be determined otherwise as it is hydrolyzed or synthesized, and thus determine the enzymatic activity of the tissue. Coenzyme A has thus been demonstrated in a variety of plant tissues, based on an assay developed on breast muscle. Coenzyme Q--a lipid-soluble-quinone involved in the electron transport system of beef heart mitochondria was demonstrated in spinach leaves and roots, Pandanus roots, roots and shoots of Corn seedlings.

The function of trace elements as coenzymes or enzyme activators in particular reactions has been pursued with profit. Determination of specific enzyme activity has been used as a basis for showing copper and iron deficiency (ascorbic acid oxidase--copper; catalase--iron).

The use of pectic enzymes obtained commercially for the separation of fairly large sheets of leaf or stem cuticle is interesting and offers challenging possibility for further information concerning this chemical substance.

5. The excellent facilities for controlled growth of plants at the Aerhart Plant Research Laboratory are the finest known to this time. The variables controlled are probably far more extensive than are possible for any or all of us, but consideration of the techniques of control should be investigated where these can be incorporated into our building plans for the future. The various methods of graphically representing growth variation by Went and his workers in their reports is suggestive and should be helpful. The realization that night temperature is of great significance in plant growth, I believe, was first presented by this group.

The new monograph by the Amer. Society of Plant Physiologists on Growth and Differentiation in Plants brings knowledge on many phases of plant growth up to date, chiefly in the newer areas of hormones, photoperiodism, vernalization and pathogen-host relationships.

Leopold wrote a very good handbook on Auxins and Plant growth for researchers and others interested, so that those working in applied biological fields might have fundamental principles in mind as they attack related or peripheral problems involving stimulation or inhibition of growth. The wave of commercial application of growth stimulators that followed the realization that 2,4-dichlorophenoxyacetic acid greatly stimulated the growth of dicot plants has not diminished in this present day of the use and misuse of Gibberellic acid. Under proper control these stimulators offer tremendous possibilities for improved cultivation practices; and their misuse has led to some stringent regulations by the Federal Pure Food and Drug Administration. The same comments apply to the use of maleic hydrazide on the inhibition of elongation growth. At proper concentrations the compound is a boon to horticulturists, ornamental plant producers and agronomists, but extremely bizarre results have followed their careless misuse. The review article by Stowe and Yamaki summarizes much of the work presented on the gibberellins. The mechanism of auxin action of gibberellic acid is still not clear.

The contrasts in nitrogenous compounds in rapidly growing vs. non-growing tissues of the same organism reported by

Steward, et. al. show the main compound that differs to be hydroxy-proline, a constituent of collagen. The storage forms of nitrogen, asparagine, glutamine, and arginine were reduced to negligible amounts in rapidly growing tissues.

The culture techniques for growing plants, large or small, under sterile conditions are adaptable for use on a number of the drug plants and offer possibility for worthwhile problems in our field.

6. The growth of isolated plant parts suggested by Haberlandt in the 1880's was first successfully accomplished by carrying isolated tomato root tips through 20 or more transfers of nutrient solutions, after which the morphology was just as typical as the original and the growth rate had increased markedly.

Much of the tissue grown as isolated tissue cultures has been removed from cambium which retains its meristematic activity. Another source has been callus stimulated to proliferation by the bacteria Mycobacterium tumefaciens of the Crown Gall tumors of several organisms. Once stimulated, the cells continue to divide and proliferate, or even differentiate to normal shoot or root under appropriate environmental conditions.

Raggio et. al., reported the formation of nodules on isolated legume roots where the inoculating bacteria were also present in the culture medium.

Steeves has carried the work on to the growth of excised leaves of several ferns in culture, though the normal differentiation terminated the growth.

The report is given of a very interesting culture of isolated single cells of carrot root phloem and their development into colonies and eventually into fully differentiated shoot or root of the carrot plant. This brings to the ultimate, the dream of Haberlandt, namely, the isolated growth of a single cell to the fully differentiated structure.

The relationship between the growth rate of tobacco root tissue cultures and their synthesis of nicotine is reported by Solt as a constant during the period of active growth. This leads to interesting conjecture. Active growth of belladonna root tissue cultures in our experiments was not accompanied by the production of the belladonna alkaloids in detectable amounts.

This technique should be an excellent tool for the study of "particular compound" synthesis and bids well to be expanded in the near future.

7. Environmental effects on the growing plant or animal are really some of the variables affecting growth and should be considered under that category. The effect of night temperature has already been referred to. In addition, certain environmental effects have been produced as by-products of practical maintenance techniques and have been developed where a desirable result was found. The use of petroleum oil in sprays is an example. and several effects are reported where this is the variable.

Flooding has been a severe problem in various parts of our country in recent years. A group of papers report information found through careful consideration of crop plants involved in such flooding.

Many of us make amused remarks about the smog over the southwestern cities. A series of papers has emerged about the physiological action of these air borne gaseous pollutants, and it is interesting to note that the choice of a test plant for assessing damage in the affected areas is the common annual bluegrass, Poa annua which grows almost everywhere in our country. More rigorous controls of airborne contaminants is needed in most or our metropolitan areas, and the success of several cities in cleaning up their air pollution gives ample evidence that this is possible and desirable.

8. Mineral nutrition of the higher plants has been investigated since any physiological work has been reported, yet there are many new factors reported. The latest review--1959 by Broyer and Stout--poses several problems about the common "macro" elements that have yet to be worked on.

Recent work of interest definitely pins down functions of the "micro" nutrients to specific roles in enzymatically regulated reactions in the plant, though there are still a number of the more common "foliar diagnosis" reports of deficiency effects in particular economic plants.

The introduction of the chelated forms of cations has been of significant value in keeping ions such as iron, manganese, copper and zinc freely available to the plant

tissue regardless of the pH and degree of particle aggregation of the soil or nutrient solution.

The difficulties involved in the proof of essentiality of a micro-element are great, and one only appreciates the magnitude of such a problem when he attempts to prepare a growth medium completely free of an element that is needed in one or two parts per million for adequate growth.

My personal interest in the effects of boron deficiency on growth is reflected in the number of references on the effects of boron on plant growth. Several experiments show this to be a fertile field for work on the constituents of our interest.

World population trends and the economics of food supply have stimulated interest in the mass culture of algae and yeasts. It has been reported that the unicellular alga Chlorella produces a higher percentage of protein per gram of tissue in a short time period than any other living organism. The only essential group of foods not produced in quantity by this organims is the vitamins, therefore the production in mass quantities of green algae and a common yeast have been suggested and tried on pilot scale as a food supplement for human consumption. Nutritionally this is a good thing--flavor wise it probably leaves much to be desired.

9. Two problems that have intrigued plant physiologists for many years have been the methods by which large volumes of water are moved to the tops of tall trees through non-living conduction tubes, and how organic matter moves through phloem tissue at the rapid rate it appears to pass. The first four articles reported indicate that there are current ideas on this problem that may, with experimental treatment, advance our knowledge.

The use of radioactive ions and counters or radioautographs have added much to the information on translocation of growth-factors, vitamins, auxins, etc. The predicted florigen which is still only a theory will probably be proved by this method.

10. Problems of pathogenicity involving fungi and viruses attract interest particularly among those depending directly on the host plant for some substantial reason. The progressive

advance of verticillium wilt on peppermint across New England, New York, Michigan and Indiana has witnessed dozens of studies on the control of the organism and resistance of the host, but the crop is virtually wiped out in these areas.

Katherine Esau's clear representation is interesting. Her contention is that one can never properly describe or analyze an effect unless he compares the diseased form with the corresponding healthy one. This would seem obvious but gross errors have been presented in the journals on this point.

Bawden's reviews seven years apart show ample evidence that plant virus diseases are primarily disturbances of the host's nucleoprotein metabolism. The infection process amounts to a separation of the nucleic acid from its protein and the breakdown of the protein. This is commonly evident in mosaic and yellows of leaves and tender stems where palisade tissue reverts to an isodiametric mesophyll and the chloroplasts do not develop along normal lines and/or disintegrate. The host cell's metabolism drastically affects the virus and the converse is just as drastically true. At this stage not enough is known to relate virus multiplication to symptom production in any of the virus diseases.

The fungicide "Captan" is considered effective in protective action against fungus and virus diseases. Certain of its methods of control are discussed by Dugger et al.

Chemotherapy in plants appears to be divided among (a) compounds that act directly on the pathogen, (b) compounds that neutralize a toxin produced by the pathogen, and (c) compounds that act on the host plant to increase resistance to the disease--such are called systemic therapeutic agents. They are further classified as topical, systemic agents for local infections and systemic agents for systemic infections. Problems of entry into the plant and translocation throughout are broad but have been attacked from many angles. The hope for a universal systemic insecticide and fungicide exceeds the experimental accomplishments to date.

11. Newer studies on plant morphology and anatomy are centered around the organization of the vegetative shoot apex vs. the flowering shoot apex, and the pattern involved in production of the mature structures; histological ontogeny and how this is related to the gross work that was reported much earlier.

Electron microscope studies of cell walls and the various cell parts offer a clearer picture of the individual structures. Those reported here are mitochondria, starch grains, fibers, sclereides, cork cuticle. There is still much good work that can be done in this area of investigation.

12. The number of compounds that could be considered in this category is limitless and the problem is to select rather than eliminate.

I have chosen nitrogenous components first because these are involved in all protein synthesis, and without this you simply have no plant to consider. The number of amino acids present in the free-uncombined fraction is only 3% to 15% of the total, and the variation much wider than that of the protein, which appears to be quite constant regardless of experimental treatments to which the plant is subject. A constituent of the fern apex that was not found in apices of angiosperms was g-hydroxy-g-methyl glutamic acid. Relationships of this compound have not yet been shown.

Each of the other compounds listed could be explained in detail and each is interesting in that it has a bearing on plant nutrition and metabolism. We will have to save this discussion until a later meeting.

(Copies of the bibliography were distributed at the Seminar. A few additional copies are still on hand and may be obtained from F. A. Crane until the present supply is exhausted.)

DISCUSSION

Gibson: Why did you limit yourself to four journals?

Crane: I considered these four readily available to our people and applicable.

Voigt: It might be pointed out that many of our people don't use these journals. They are a good place to begin reading on this phase of the work. The pharmaceutical journals were not used because it is assumed that you do follow these.

Crane: These are standard journals and should be read by our people--some of the others might be excusably overlooked.

Dunn: Have you come across much literature on the absorption of CO_2 by roots?

Crane: There are references on absorption--certainly CO_2 is absorbed freely by roots as bicarbonate and not as the gas. I would say there has been some interest in the absorption of bicarbonate by roots.

Albers: Have you come across photosynthesis of natural products, antibiotics, isolated chlorophyll as affected by sunlight?

Crane: Do you mean isolated chloroplasts?

Albers: Isolated chlorophyll.

Crane: This refers to the work of Baly in England. Arnon at California has shown photosynthesis by isolated chloroplasts but the magnitude is extremely small.

Albers: I understand that some Germans have synthesized ascaridol from a compound in the presence of light.

Ramstad: They have used chlorophyll as a catalyst for this reaction.

Claus: What is the source of the Journal of Experimental Botany?

Crane: British Publication of the Clarendon Press, about 6 years in publication.

Cougher: You made reference to Chlorella as having the greatest growth and synthetic rate- what is this rate?

Crane: for Chlorella, from 100 cells to several million cells in three days.

Cougher: Certain bacteria will increase to this number in several hours.

Crane: Growth rate is greater but food material is used up rather than synthesized, whereas Chlorella produces new organic matter during this time--it is the synthetic rate which is claimed as greatest.

PHYLOGENY AND CHEMICAL CONSTITUENTS

Varro E. Tyler, Jr.

"...While we are only at the beginning of phytochemical knowledge, the phylogenetic value of phytochemistry is already considerable."
W.B. Turrill, 1942 (1)

Although scientific observations regarding the occurrence of chemically related constituents in phylogenetically related plants were made as early as the 17th century and the basic principles requisite for the development of chemotaxonomy were clearly stated 150 years ago (2), botanists and chemists alike have shown comparatively little interest in this field of knowledge, and it remains a neglected but challenging area for study and research. The reason for this neglect is apparent when one considers the tendency toward specialization of knowledge and the fact that few chemists are adequately trained in botany and few botanists in chemistry. By its hybrid nature, chemotaxonomy becomes a fruitful field of endeavor for scientists with inter-disciplinary training, and it is not surprising that pharmacognosists have made important contributions to its development and remain as the best qualified and most likely individuals to further its future development.

It should be emphasized at once that it is very unlikely that information based on chemical analysis will ever replace that obtained from a study of form and structure in routine identification and classification of members of the plant kingdom. Even if we foresee analytical methods of the future which are as advanced in comparison to present-day techniques as paper and gas chromatography are to the classical methods of plant analysis, morphology and histology will still play dominant roles in taxonomic botany. However, the importance of chemical analysis as a tool of great value in determining true phylogenetic relationships can no longer be doubted, and in the herbarium of the future it will be as unthinkable to omit a detailed chemical analysis of the specimen in question as it would be today to omit the preservation of leaves and flowers of a plant.

Today, it is generally acknowledged that plants which are closely related phylogenetically are also closely related in their chemical constituents. However, it is also realized that many chemical components of plants are widely and apparently non-uniformly distributed, and it becomes necessary to

determine which of the various compounds are useful for classification purposes. The principle formulated by De Candolle, that only specific plant constituents (tannins, bitter principles, volatile oils, resins, etc.) are useful for this purpose was widely accepted for many years. A principle related to this hypothesis is the so-called "frequency rule" (3) which was formulated from the observation that compounds of relatively simple structure are more widely distributed than those with complex structures. The complex derivatives were believed to be characteristic of either a family, genus or species. In many cases this is true, and examples are numerous. The closely related genera Cinchona and Remijia are the only reported sources of the complex alkaloid, quinine, in the entire plant kingdom. However, recent investigations have shown that many of the "general" constituents (protein, lignin, carbohydrates, etc.) are also of considerable value in determining plant relationships. Thus, we cannot take, without additional evidence, either the sporadically or the ubiquitously occurring compounds as a guide to the classification of plants. To do so would be just as artificial as the attempts at classification on the basis of the form of the leaf or the number of stamens (4).

What, then, are the types of chemical compounds which have demonstrated their usefulness in the classification of plants? Proteins appear to be one of the most useful, but because of their chemical complexity, one of the most difficult groups with which to work. For example, it has been established that prolamines occur only in the Gramineae. This becomes a characteristic as typical of this family as any morphological feature yet established. Furthermore, prolamines have been found to be species specific, differing slightly in structure in the various species of the different genera which make up the grass family.

Because of the difficulty in isolating and determining the composition of compounds of this type, indirect methods have been applied to distinguish them. For a number of years, plant serology was extensively employed and yielded results which for the most part have supported existing concepts of plant relationships.

In these studies immunological principles were applied. This generally involved the injection of a proteinaceous extract obtained from the plant in question into a test animal, usually a rabbit, to produce specific antibodies in that animal's serum. Then the serum was tested against

proteinaceous extracts of other plants and the degree of reaction, usually precipitation, was taken as indicative of the degree of relationship of the two plants. By plotting the results in the form of circles of greater or lesser radii according to the strength of reaction and observing the degree of intersection of circles from two or more centra, it was possible to construct a phylogenetic tree which is indicative of the evolutionary relationship of all members of the plant kingdom. Since this tree was worked out by Mez and his colleagues in Königsberg, it has become known as the Königsberger Stammbaum (5). Much valuable information is to be obtained from a study of this interesting scheme which, as a whole, exemplifies the unity of life and the absence of convergence in protein evolution.

Two excellent reviews of plant serology have appeared (6,7), and in reading them, it is difficult to understand why in recent years the application of serological methods has been restricted to animal and virus experimentation. Here is a challenge to the pharmacognosist who, practically alone among modern scientists, is equipped to apply these extensively developed and evaluated procedures to the investigation of plant relationship.

One of the few taxonomists to employ serological data, among others, in the compilation of his classification system was von Wettstein. (8). For this reason, it is generally conceded that his system is much more nearly phylogenetic in arrangement than many others. Although von Wettstein's work is much admired and widely quoted by our European colleagues, it has been largely ignored in this country, and his important Handbuch has never even been translated into English.

A more novel method of determining related plant proteins has been systematically investigated in Russia. A. W. Blagowestchenski (9) has reported the results of his studies on the effect of evolution on the activation energy of enzymes. According to this investigation, the activity of a given enzyme is greater, the higher the plant on the phylogenetic scale. That is to say, primitive plants possess enzyme systems which are less efficient than those of higher plants in utilizing respiratory energy. Oddly enough, Blagowestchenski's methods appear never to have been employed by American researchers in plant biochemistry or taxonomy.

Lignin is another widely occurring plant constituent which appears to be of great value in establishing plant

relationships. It has evolved from a methoxy-free state in the bryophytes to a methoxy-rich state in the angiosperms. As would be expected, most pteridophytes and gymnosperms have been found to be intermediate in this regard. Furthermore, it has been shown that these phylogenetic characteristics of lignin are very impressively recapitulated during ontogenesis (2). Other constituents of wood have been investigated and shown to be useful in the differentiation of species of conifers (10).

Obviously, there is not always a continuous change in the properties of a type of compound with an increased stage of development. This is perhaps best exemplified by the types of reserve carbohydrates found in plants. The same compounds, glucose, fructose, sucrose and starch are found in all orders of green plants from the highest to the lowest. Yet, numerous groups show a variation in this basic pattern; for example, inulin occurs spasmodically in many families ranging from the green algae and mosses to the Compositae. This is obviously an example of parallel or convergent evolution of chemical characteristics. The storage of glucose, fructose, sucrose and starch must therefore be considered as a primitive characteristic, and taxa which have changed over to a different type of carbohydrate reserve are situated on side tracks of evolution (2). There are, nevertheless, a sufficient number of these to render the nature of the carbohydrate reserves in plants as valuable taxonomic features. A recent report on the water-soluble carbohydrates found in the seeds of the Gramineae (11) showed that on this basis alone it was possible to distinguish absolutely over half of the species examined. Since the water-soluble carbohydrates comprise less than 5% of the dry weight of seeds, it is suggested that detailed study of other components might yield results of far-reaching taxonomic importance.

The same type of specialization of chemical constituents appears repeatedly in plants, but so do certain morphological and anatomical characteristics. Because of this, it is extremely important to examine critically the significance of each particular type of compound in tne investigation of plant relationships. Although this is particularly true of the so-called general constituents, it also applies to the specialized types of compounds.

As mentioned previously, it was long believed that only the specific plant constituents were of classificational significance. It is not surprising, therefore, to find a

majority of chemotaxonomic works dealing with these compounds.

The occurrence of tannins in the plant kingdom has been extensively investigated by Bate-Smith and Metcalfe (12), and they have compared their findings with various taxonomic schemes and reported the results. It is concluded that tannins can be used as a taxonomic character, and that all dicotyledenous plants may be divided into three groups: 1. families in which nearly all species are tanniferous, 2. families in which tannins are of very limited occurrence and 3. mixed families. Comparison of these results with established plant families shows that tannin synthesis in dicots has evolved in a manner which corresponds to a marked extent with our present concepts of plant families. There are even some points of agreement between arrangement of families in orders and capacity to synthesize tannins, but extensive agreement is not to be expected in this area due to marked differences of opinion in the various classificational schemes concerning the composition of orders.

In regard to the phylogenetic significance of tannins, they found, by comparing the occurrence of tannins with the "advancement index" assigned to plants by Sporne, that ability to synthesize tannins is a primitive character that tends to become lost with increasing phylogenetic specialization.

Hegnauer (13) has investigated the occurrence of cyanogenesis in 400 species of plants and has discussed the taxonomic significance of this phenomenon. Cyanophoretic compounds occur less frequently than alkaloids, and at present their taxonomic significance is limited, but they may become more important once the identity of all such compounds is established. As a rule, a genus or tribe contains the same cyanogenetic compound, but certain families are known to produce different compounds.

Recently, Stafford (14) has reported the results of her investigations on the occurrence of tartaric acid in the leaves of a number of species. Although tartrate may be found in trace amounts in a widely distributed number of angiosperms, it is accumulated in large quantities in perhaps only three different families, the Vitaceae, the Geraniaceae and the Leguminosae. The genetic factors controlling this large scale accumulation must have arisen independently in each group since some closely related forms do not possess this characteristic. It is concluded that within these different taxa the content of tartaric acid can be used as a characteristic of taxonomic value.

Specific nitrogenous compounds have proven particularly valuable for chemotaxonomic purposes. A recent study (15) has shown that the principal free amino acids in plants are family characteristics. For example, arginine is the principal amino acid in the Saxifragaceae and the Rosaceae, but citrulline occupies this position in the Betulaceae and Juglandaceae. Acetyl ornithine appears to be characteristic of the subfamily Fumarioideae (Papaveraceae).

Compounds of this sort appear to be of particular value in settling classificational problems among certain genera of the Agaricaceae which are especially difficult to distinguish by classical methods. Unpublished work of the author has revealed that the biogenic amine serotonin and its precursor, 5-hydroxytryptophan, are characteristic of the genus Panaeolus. Members of this genus are, according to Singer (16), determinable with difficulty by the expert and not at all by the layman. For some time a controversial point has been the distinction between Panaeolus campanulatus and Panaeolus sphinctrinus (17). Recently, it has been shown that the latter species contains the active hallucinogenic principal, psilocybin (18), while unpublished data of the author indicate that this compound is not present in the former species. Thus, by the presence of nitrogenous compounds of relatively simple structure, it is possible to settle objectively questions of classification not amenable to clear-cut subjective decisions.

Of all the nitrogenous compounds found in plants, the alkaloids compose the group which has been investigated most extensively for its taxonomic and phylogenetic significance. The fact that these compounds accumulate in appreciable quantites in nearly one-sixth of the known species of higher plants, plus the relatively complex chemical structures of many of them, places the alkaloids in a position of undoubted importance in the field of systematic botany.

An example of the application of the occurrence of an alkaloid in verifying taxonomic postulations is seen in the case of colchicine (19). This alkaloid apparently exists in about 15 different genera, all of which belong to the Liliaceae in the sense of Krause as set forth in "Die naturlichen Pflanzenfamilien", 2nd ed., 1930. Now, Hutchinson, whose taxonomic system has gained wide acceptance because of its modern approach, has argued that Krause's concept of the Liliaceae is too broad, and that certain groups should be removed from it and placed in other families. For example, those plants with umbellate inflorescences should be consigned

to the Amaryllidaceae. If the genera which contain colchicine are re-examined, it will be found that all of them fall in subfamilies which are left in the family Liliaceae by Hutchinson; that is, no plants are known to contain the alkaloid which are outside of the Liliaceae in the sense of Hutchinson. The distribution of this alkaloid strongly supports his revision of this plant family.

Another example of the usefulness of alkaloids in deciding taxonomic issues is found in the case of protopine and the Papaveraceae (19). This family in its broad sense is divided into three subfamilies, Papaveroideae, Hypecoideae, and Fumarioideae. Hutchinson considers the latter group sufficiently distinct to be considered as a separate family, the Fumariaceae, concluding that its members did not arise directly from ancestors of the present Papaveraceae. Manske, on the other hand, points out that no plant of the entire Papaveraceae family has been found to lack alkaloids and one alkaloid, protopine, occurs in every plant. Of even greater importance is the fact that with one possible exception, protopine has not been found in plants of other families. Manske concludes that all three subfamilies of the Papaveraceae are closely allied chemically and argues for the retention of the broad concept of the family.

Employing available data on the biogenesis of alkaloids, Hegnauer (20) has established a system of "alkaloidal families" under which the various plants containing these compounds may be classified. The families total eight in number and include derivatives of 1. phenylalanine, 2. tryptophan, 3. ornithine, 4. lysine, 5. histidine, 6. anthranilic acid, 7. nicotinic acid and 8. compounds not related to amino acids, which he entitles "alkaloida imperfecta".

By grouping the plants which contain alkaloids under these headings and analyzing the results, he is able to draw some interesting conclusions. For example, in higher plants the more complex alkaloids of the tryptophan type are found exclusively within the Loganiaceae, Apocynaceae and Rubiaceae. This indicates that taxonomists like Hallier and Hutchinson who derive the Rubiaceae from loganiaceous-like ancestors are probably correct in their interpretation. Ornithine-derived alkaloids of the hygrine type are especially concentrated in the Erythroxylaceae, Convolvulaceae and Solanaceae. This speaks for a close genetic relationship between the three families. The derivation of the Tubiflorae from plants of the linacious type (with which the Erythroxylaceae is very

closely related) has been discussed by von Wettstein. This is very strongly supported by phytochemical evidence.

In addition to a study of the taxonomic and phylogenetic significance of general or specific plant constituents per se, it appears to be possible to derive much important data from proper statistical consideration of groups of these compounds, McNair (21) was apparently the first to employ such methods, considering the phylogenetic importance of such features as the average molecular weight of alkaloids and the average iodine number of fats for entire families and orders. From this he has drawn some rather sweeping conclusions with regard to the primitive or derived nature of a chemical characteristic. For example, if starch is the characteristic reserve of a seed, this is considered as a primitive characteristic; the presence of a fatty oil would be indicative of an advanced state. Low iodine number, less fatty acids and the presence of short chain fatty acids in a seed oil are likewise primitive; high iodine number, more fatty acids, and longer chain length are derived features. Alkaloids of low molecular weight are said to be primitive characteristics as opposed to the advanced nature of high molecular weight alkaloids. Unfortunately, some of these postulations are not conclusive (2). Molecular weight is no measure of the complexity of biosynthesis of an alkaloid, but is merely indicative of the size of the components which form it. Also, the value of McNair's work is diminished by an insufficiently critical treatment of the phytochemical literature. Nevertheless, the method remains as one which should prove of considerable future value in the study of chemical phylogeny.

Numerous problems confront the investigator in the field of chemotaxonomy. By far the largest task which will hinder, until completed, the development of the science is the elucidation of the structure and identity of the chemical constituents of each member of the plant kingdom. Although certain divisions of it are now rather well-worked, others have been scarcely investigated; the feat is a herculean one but one which must be accomplished. Considering that the accumulated knowledge of mankind in the last few decades is equal to all the knowledge compiled before that time, the task does not seem as formidable as at first glance.

Not the least of the problems facing the investigator in chemotaxonomy is the lack of a reliable, up-to-date compilation of the occurrence and distribution of chemical compounds (even those of a secondary nature) which have already been

discovered in the plant kingdom. Although compendia, such as those of W. Karrer (22) and Schermerhorn and Quimby (23) are welcome additions to the literature and distinctly useful in certain types of phytochemical and pharmacognostical investigation, neither is sufficiently complete to fulfill the needs of the taxonomist in search of information upon which to decide classificational matters.

Another difficulty is that which confronts the analyst in deciding whether or not a particular chemical entity occurs in a plant system. Reverting to the "frequency rule" it has been established that compounds of relatively simple structure are more widely distributed than those of complex structure. The rule would also indicate, although it is exceedingly difficult to prove, that many relatively simple but infrequently occurring compounds are commonly synthesized in many plants, but only as intermediate metabolic products which do not accumulate in sufficient quantity to permit detection. This explanation has been advanced to explain the widespread but spasmodic occurrence of nicotine in the plant kingdom (24). Actually, analytical studies are restricted primarily to products which the organism accumulates, and this may not be truly indicative of the organism's synthetic ability. Based upon this consideration, Hegnauer has arbitrarily concluded that, in the case of alkaloids, plants which accumulate less than 0.01% on a dry weight basis should be considered as alkaloid-free (20).

Another factor which renders difficult the accurate application of chemotaxonomic methods is the non-homogeniety of various plant taxa. Members of some groups are very closely related taxonomically, others to a much lesser degree. The establishment of variable chemical criteria to fit these existing situations is extremely difficult.

A task which is difficult to accomplish must offer some reward for its achievement to be worthwhile; chemotaxonomy is no exception. Aside from its usefulness as an objective tool in the establishment of the evolutionary pattern of the plant kingdom, the discipline offers certain practical applications of immense importance. It will assist in the prediction of the occurrence of certain chemical compounds, enabling new sources of supply of drugs and drug precursors to be located with a minimum of effort. It will permit a more exact classification of groups of plants not readily distinguished one from the other. So-called chemical races or varieties are known to occur among

species of many medicinal plants, and these plants with similar phenotypes but different genotypes are identical in external appearance (25). The variation of their chemical constituents can be of considerable commercial importance. Consider the case of ergot. Sclerotia of this fungus produced on a single host plant are quite uniform in appearance, but it has been shown (26) that at least six chemical races are distinguishable on the basis of the qualitative nature of the alkaloids produced. Obviously, selection of the proper strain for the desired alkaloid becomes an important consideration in the production of this drug. The classical example of chemical races in higher plants remains the genus Eucalyptus in which the composition of the volatile oil can vary appreciably in different physiological forms (27). More recently, the selection of chemical races has become of importance in the production of tropane alkaloids from species of Duboisia (28) and in opium and digitalis production.

It is thus seen that in certain instances it is possible to distinguish plants from one another chemically when morphological and histological features are not conclusive. Chemical constituents also are destined to play an important role in helping to decide objectively questions in taxonomy and phylogeny which cannot be answered satisfactorily on the basis of subjective evidence. Although there are certain difficulties involved which stem primarily from a paucity of knowledge (and its dissemination) regarding the constituents of plants, chemotaxonomy appears to be a fruitful area for scientific research. Because of his unique training in the disciplines of chemistry and biology, the pharmacognosist is admirably suited to play an important role in the development of this science of the future.

REFERENCES

(1) Turrill, W.B., Botan. Rev. 8, 247,473,655 (1942).
(2) Hegnauer, R., Pharm. Acta Helv., 33, 287 (1958).
(3) Paech, K., "Biochemie und Physiologie der sekundaren Pflanzenstoffe," Springer-Verlag, Berlin, 1950, p.29.
(4) Hansel, R., Arch. Pharm., 289, 619 (1956).
(5) Gortner, R.A., "Outlines of Biochemistry," 2nd ed., John Wiley and Sons, New York, 1938, p. 542.
(6) Chester, K.S., Quart. Rev. Biol., 12, 19,165,294 (1937).
(7) Moritz, O., in "Encyclopedia of Plant Physiology," Vol.8, ed. by Mothes, K., Springer-Verlag, Berlin, 1958, p. 356.

(8) Wettstein, R.von, "Handbuch der systematischen Botanik," 4th ed., Leipzig and Vienna, 1935, p. 1152.
(9) Blagowestchenski, A.W., "Die biochemischen Grundlagen des Evolutionsprozesses der Pflanzen," Akademie-Verlag, Berlin 1955.
(10) Erdtman, H., in "Wood Chemistry," 2nd ed., Vol. 1, ed. by Wise, L.E., and Jahn, E.C., Reinhold Publishing Corp. 1952, p. 661.
(11) Mac Leod, A.M., and McCorquodale, H., New Phytologist, 57, 168 (1958).
(12) Bate-Smith, E.C.and Metcalfe, C.R., J. Linnean Soc. London, Botany, 55, 669 (1957).
(13) Hegnauer, R., Pharm. Weekblad, 93, 801 (1958).
(14) Stafford, H.A., Am. J. Botany, 46, 347 (1959).
(15) Reuter, G., Flora (Jena), 145, 326 (1957).
(16) Singer, R., Schweiz. Z. Pilzkunde, 6, 81 (1958).
(17) Singer, R., and Smith, A.H., Mycopathol. et Mycol. Appl., 9, 280 (1958).
(18) Heim, R., and Wasson, R.G., "Les Champignons Hallucinogènes du Mexique," Museum National d' Histoire Naturelle, Paris, 1958, p. 262.
(19) Gibbs, R.D., Trans. Roy. Soc. Can. V, 48, 1(1954).
(20) Hegnauer, R., Planta Med., 6, 1 (1958).
(21) McNair, J.B., Lloydia, 8, 145 (1945).
(22) Karrer, W., "Konstitution and Vorkommen der organischen Pflanzenstoffe," Birkhäuser Verlag, Basel and Stuttgart, 1958, pp. 1207.
(23) Schermerhorn, J.W., and Quimby, M.W., "The Lynn Index," Monographs I, II, III, continuing, Massachusetts College of Pharmacy, Boston, 1957,'58,'59, continuing.
(24) Hegnauer, R., in "Biochemie and Physiologie der Alkaloide," ed. by Mothes, K., Akademie-Verlag, Berlin, 1957, p.10.
(25) Evans, W.C., Pharm. J. 179, 505 (1957).
(26) Kybal, J., and Brejcha, V., Pharmazie, 10, 752 (1955).
(27) Penfold, A.R., and Morrison, F.R., in "The Essential Oils," Vol. IV, by Guenther, E., D. Van Nostrand Company, New York, 1950, p. 503
(28) Barnard, C., Econ. Botany, 6, 3 (1952).

DISCUSSION

Youngken Sr.: I was greatly interested in this presentation. In 1926 at the International Congress of Botanical Sciences in New York there was present a scientist from Germany named Karl Metz. I well recall his discussion of the general taxonomic effects which he performed as a pioneer in this line. He injected sap of one species into another and by the nature of the serum reaction he was able to show closeness or distance of the relationship of one plant to another. He apparently was a real pioneer in this field. I am happy to note the considerable progress made in this field since that time.

Redman: I did not hear any reference to the cyanogenetic group. In the case of the Rosaceae, Prunus amygdalis var. miera and P. amygdalus var dulcis have been distinguished by chemical means. In view of the opening remarks of our seminar, taxonomy is on the way out. I wonder just where the studies reported here are going to lead?

Tyler: I did not mean to slight the cyanogenetic group--you'll find references to it by Hegnauer, whose article is written in Dutch with a German summary. As to the importance of taxonomy--there is a world of difference between this work just reported and that which I teach my undergraduate students.

Dunn: What reference can you make to the volatile oils?

Tyler: Classical work was done on the genus Eucalyptus. There is a large body of work on this group. It has not been widely applied in other groups.

Dunn: How about the Labiatae?

Claus: Reference may be made to the work of Darnley Gibbs who has worked on relationships in taxonomy based on chemical constituents.

Tyler: Some work has been done on the genus Pinus, which is reported in this bibliography.

Dunn: what of the practicability of carrying things to the family by gross taxonomic means, then using the chemical approach within the family?

Tyler: The idea is admirable--to my knowledge it hasn't been done. My own personal interest is based on work I have read about.

Ramstad: You have not said anything about classification of microorganisms. Has this work been used in classification of the fungi?

Tyler: What has been said about mushrooms might apply to other fungi. Information reported about bacilli and other microorganisms has not been correlated. It is probably farther away from a clear picture than those reported.

Claus: I appreciate the difficulty Tyler has had in gathering information about this work. Those who work on such problems should be sure to get the work published. When one compares the constituents of the root of one species with those of the stem of another species of the genus, the unripe fruits of another species of the same genus etc., the problem of correlating these pieces of information is difficult.

Albers: In Tyler's opinion is the chemical classification superior to the genetic approach?

Tyler: There will come a day when every plant specimen found in herbaria will have a complete chromosome analysis as well as microchemical analysis. The taxonomists of today will throw up their hands upon hearing this. The field of chemistry is broad, as is the field of taxonomy.

BIOSYNTHESIS OF ALKALOIDS

Arthur E. Schwarting

I. INTRODUCTION

The reaction through which a cell or tissue produces an organic compound is a part of a biosynthetic system. The oxidation of a secondary alcohol function of D-glucitol to a carbonyl group, yielding L-sorbose, is an example of one reaction in such a system. Such a reaction has biogenetic implications in that it is specific configurationally and is known to be accomplished within certain species or chemotypes, of the plant kingdom. Biogenetic associations are, however, not limited to chemical reactions.

Biosynthetic systems and biogenetic relationships have been subjects for both experiment and conjecture concerning secondary plant products containing nitrogen. The specific pattern of atoms occurring in these compounds, particularly alkaloids, has provided an anatomy that has become the basis for comparison. The first logical exploration in this area was to provide a method for *in vitro* synthesis. The synthesis of tropinone from succindialdehyde, methylamine and acetonedicarboxylic acid was the first in a series of accomplishments which posed as approximate models of *in vivo* reactions.

Biogenetic considerations have aided the chemist in his approach to the synthesis of many natural products and have provided, for some, the inspiration to attempt a synthesis. Their results have, in turn, provided hypotheses which have been tested by biological experiment. For the most part these synthetic approaches have dealt with structures and not sequences. The supposed "physiological conditions" are hardly that; enzymes are not a part of the *in vitro* method. Recorded theories have violated biochemical principles by unlimited use of single carbon units or opening or closing rings without regard to theory of reaction mechanisms.

A biosynthetic reaction or a biogenetic relationship has greater significance than that a mechanism accommodates a biochemical postulate. To the biologist it is a basis for genetic and chemical character and, thus, provides an adjunct to systematics. In certain applications it has provided mechanisms of formation of organic compounds not amenable to other methods. Finally, the studies provide a broad challenge to reveal the intricacies of the living cell.

Studies on the heredity of anthocyanin substances in higher plants and on auxotroph mutants among microorganisms generated the one gene-one enzyme theory. This theory provided a basic proposition by which many transformations and relations were understood. The results of this early work significantly influenced the thinking and future work in both genetic and chemical understandings of cell metabolism.

The absolute origin and transformations leading to secondary plant principles containing nitrogen is quite obscure. That these substances are related to amino acids and that many are products of a primary reaction which yields shikimic acid is quite obvious. The fact that tyrosine is the precursor to morphine and that a moiety of the tropinone molecule is derived directly from ornithine is well established, but intermediates in the reaction, if they exist, are unknown and in these and other cases, the enzymes and their requirements are unknown quantities. Much theory is applied comparatively. Shikimic acid is hardly known among higher plants, yet it must be used to profitably present biosynthetic theory in these plants.

The architecture and relationships among the majority of alkaloids can be described by considerations involving three metabolic phenomena. They are (1) one-carbon condensation, (2) aromatization and (3) ring closure of aliphatic amino acids.

II. ONE-CARBON CONDENSATION

One-carbon and occasionally two-carbon units have consistently been used by proponents of various biosynthetic systems to provide an "equivalent" to lengthen a carbon chain or to effect ring closure. The demethylation of methionine to homocysteine, and the reversal of the reaction, typifies methyl group metabolism. Transmethylation as an aspect of the intermediary metabolism of amino acids is thoroughly understood.

Many alkaloids represent O- or N- methyl analogs of amines or amino acids and among the alkaloids certain species and biotypes are distinguished by the occurrence of methylated analogs. Hordenine (II) is the dimethyl derivative of tyramine (I) and trichocereine (IV) is the N-dimethyl analog of mescaline (III). In the biosynthesis of ricinine both O- and N-methylation results from the same biochemical mechanism. Methylation of the tobacco alkaloids has been the subject of considerable research.

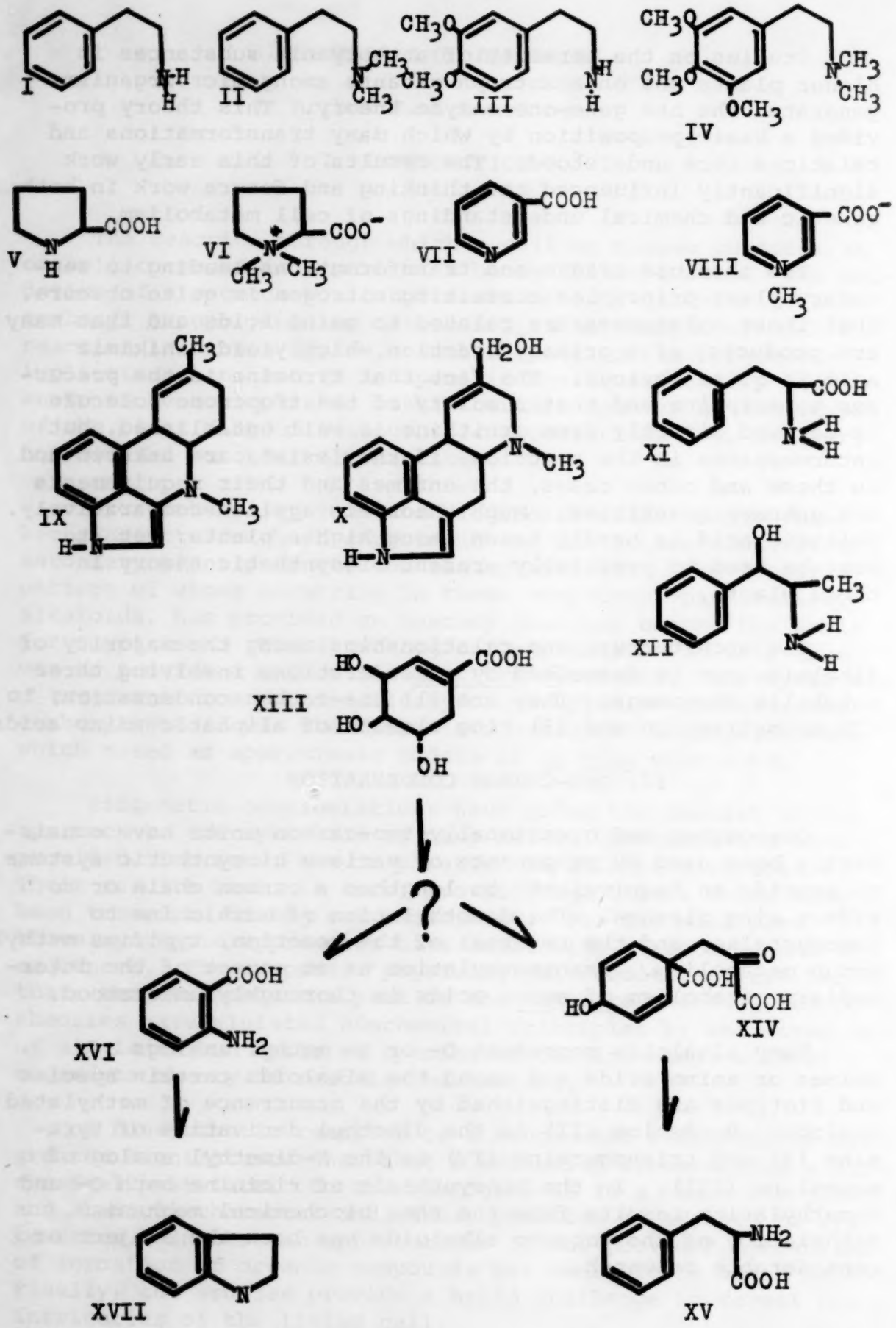


FIGURE 1

Various alkaloids represent betaines of primary amines although convincing evidence of a direct relationship is lacking. The methyl betaines of proline (V) and nicotonic acid (VII) are stachydrine (VI) trigonelline (VIII) respectively.

Several curious methyl group transformations exist which cannot be adequately described. Agroclavine (IX) is the methyl analog of elymoclavine (X), which posesses a primary alcohol function. In the bioconversion of phenylalanine (XI) to norpseudoephedrine (XII) it has been assumed that the beta carbon of the side chain is not removed but whether the carboxyl group is reduced in the process was not established.

III. AROMATIZATION

It is generally assumed that shikimic acid (XIII) is the precursor of the aromatic rings of phenylalanine (XV) and indole (XVII). Sedoheptulose-1, 7-diphosphate is the precursor of shikimic acid in E. coli. In other cell systems this acid has been shown to originate from a three-carbon glycolysis intermediate and a tetrose phosphate of the pentose pathway.

The immediate products of shikimic acid are anthranilic acid (XVI) and prephenic acid (XIV). The former is the progenitor of the pyridine nucleus and the latter is the intermediate in the pathway to phenylalanine (XV). In contrast, a sequence of reactions involving the degradation of tryptophan to nicotinic acid is well established and accounts for the conversion of indole nitrogen to pyridine nitrogen.

Associated with these products, is a series of amine oxidase catalyzed reactions which is of concern in the derivation of alkaloids. The flavin-dependent dehydrogenation of an amine yields the imine which in turn reacts spontaneously with water to form the corresponding α-keto acid. In the absence of catalase the transformation yields the next lower carboxylic acid. Mono- and diamine oxidases are not specific and either will attack both mono- and diamines.

Heterocyclic compounds have been formed by plant amine oxidase and this enzyme oxidizes phenylalkylamines as well as aliphatic diamines in the formation of pyrrolidine, piperidine and indole compounds from unnatural precursors. However, enzymatic in vitro synthesis of natural diamines offer confirming evidence for the role of these enzymes.

The condensation of a phenylethylamine analog with a phenylacetaldehyde derivative was an early model alkaloid

synthesis yielding a benzylisoquinoline analog and is now the subject of renewed interest as an *in vivo* model of a reaction that is plausable, both with regard to substrate and end product. A similar reaction involving the condensation of dioxyphenylethylamine with acetaldehyde to yield noralsoline (XVIII) has its equivalent in the biogenetic relationship which exists among the cactus alkaloids mescaline (III) and anhalonidine (XX).

The benzylisoquinoline structure contains a plurality of reaction sites and as a result a considerable number of secondary reactions are presumed to occur to account for the varied architecture among this group. The benzylisoquinoline structure is, therefore, represented by a number of alkaloids including papaverine (XX). The simple oxygenated derivative of this structure is represented by narceine (XXI) while the lactone analog of this type is represented by narcotine (XXII), a phthalideisoquinoline type.

The aporphine type occurs as a product of secondary condensation of the catechol ring with the isoquinoline moiety and more than one type is probable in that the oxidative process involves the activation of the position ortho or para to the hydroxyl. Representatives of these modifications exist in isothebaine (XXIII) and laureline (XXIV). It is probable that either may be a derivative of a tetrahydroxy precursor.

Hetero ring formation of the benzylisoquinoline structure is represented in cularine (XXV).

The protoberberine type, berberine (XXVI), is in all probability an intermediate type between the parent benzylisoquinoline substance and the protopene type, cryptopine (XXVII) and biogenetically the protoberberines and the phthalideisoquinoline structures must be considered inter-related.

The biochemical origin of the naphthaphenthridine alkaloids, e.g., sanguinarine, together with lycorin and members of the erythrinoidine type is difficult to determine. Each involves a ring cleavage transformation that has negligible counterparts in other known biochemical expression.

The biosynthesis of morphine has been established through studies involving the use of α-C^{14}-tyrosine and phenylalanine. The skeleton of the benzylisoquinoline alkaloids, showing the phenylalanine moieties is represented in structure XXVIII. By rotation of the isoquinoline moiety as shown and by ring closure through oxidation at the designated position, the morphine molecule (XXIV) is obtained with the labeling as indicated.

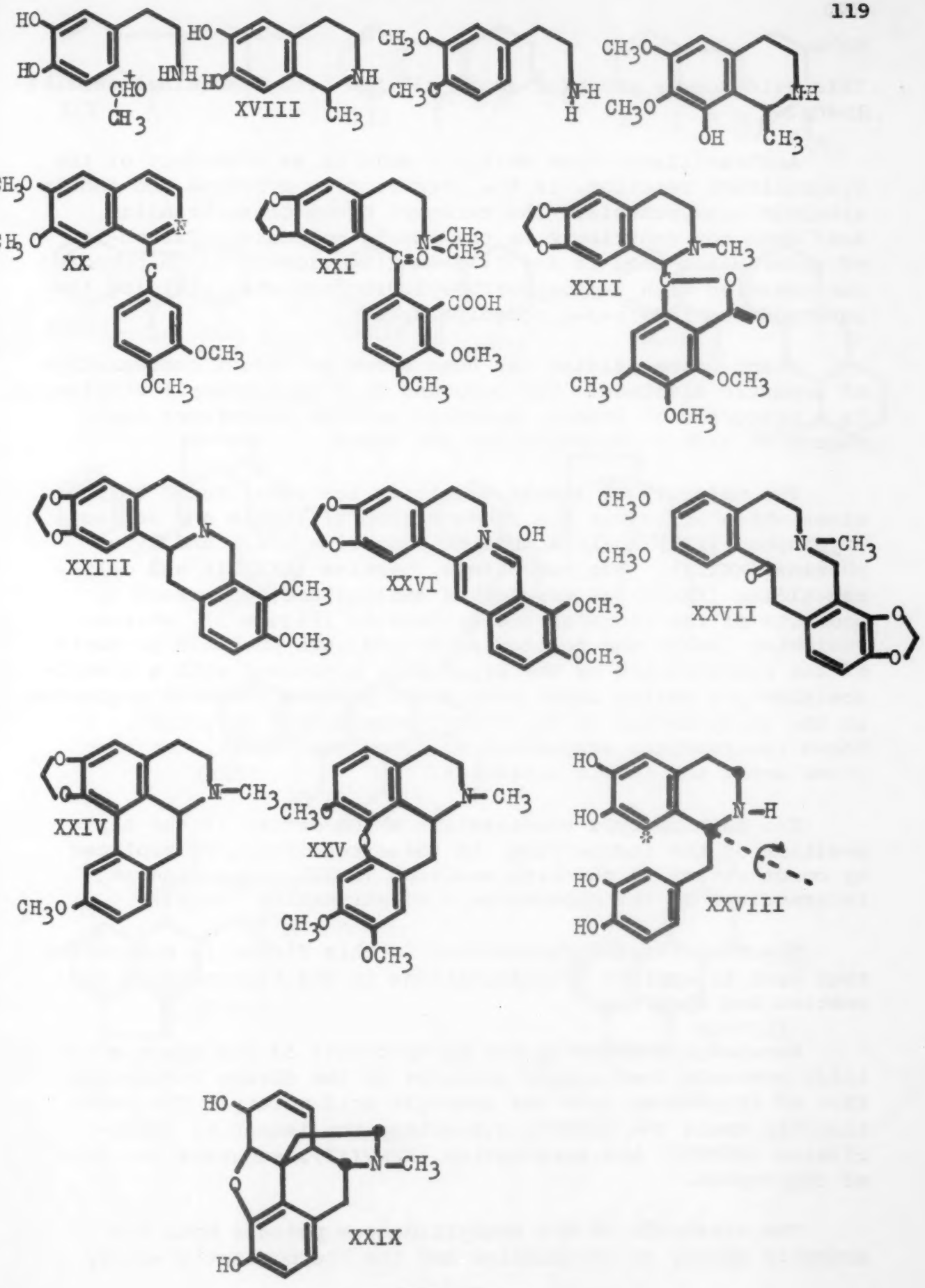


FIGURE 2

This evidence is singular among all the benzylisoquinoline alkaloids.

Anthranillate, from shikimic acid or as a product of the kynureninase reaction, is the precursor in pyridine and indole alkaloid biosynthesis. The carboxyl group of anthranilic acid does not contribute to the indole molecule. Carbon-1 of anthranilic acid is involved in ring closure via a proposed condensation with 5-phosphoribosylpyrophosphate, yielding the intermediate indole-3-glycerolphosphate.

Plant amine oxidase has been shown to effect condensation of aromatic diamines. The compound 2-(2-aminophenyl) ethylamine is a precursor of indole, however, natural precursors equivalent to such a structure are not known.

The majority of indole alkaloids are substituted tryptamines which arise via the condensation of indole and serine. Tryptophan (XXX) analogs include dipterine (XXI) and hypaphorine (XXXII). The carbolines, harmine (XXXIII) and calycanthidine (XXXIV) as tryptophan analogs are equivalent to products of the isoquinoline biogenesis (Figure 3), whereas yohimbine (XXXV) and related alkaloids, are probable products of the condensation of the tryptophan precursor with a phenylacetaldehyde analog under conditions similar to those operative in the biosynthesis of the benzylisoquinoline structure. No known intermediate equivalent to narcotine (XXII), has been found among the indole alkaloids.

The Mannich-type condensation which occurs in the alpha position of the indole ring, in these reactions, is replaced by condensation in the beta position (XXXV) to provide an intermediate in the biosynthesis of strychnine (XXXVI).

The ring fission represented in this figure is not unlike that used to explain transformations in the biosynthesis of emetine and ajmaline.

Knowledge concerning the biosynthesis of the ergot alkaloids presents conflicting evidence on the direct incorporation of tryptophan into the lysergic acid moiety. The relationship among the clavine alkaloids, the isomer of chanoclavine (XXXVII) and agroclavine (XXXVIII), suggests the role of tryptophan.

The alkaloids of the Amaryllidaceae possess both the aromatic moiety of isoquioline and the hydroaromatic moiety

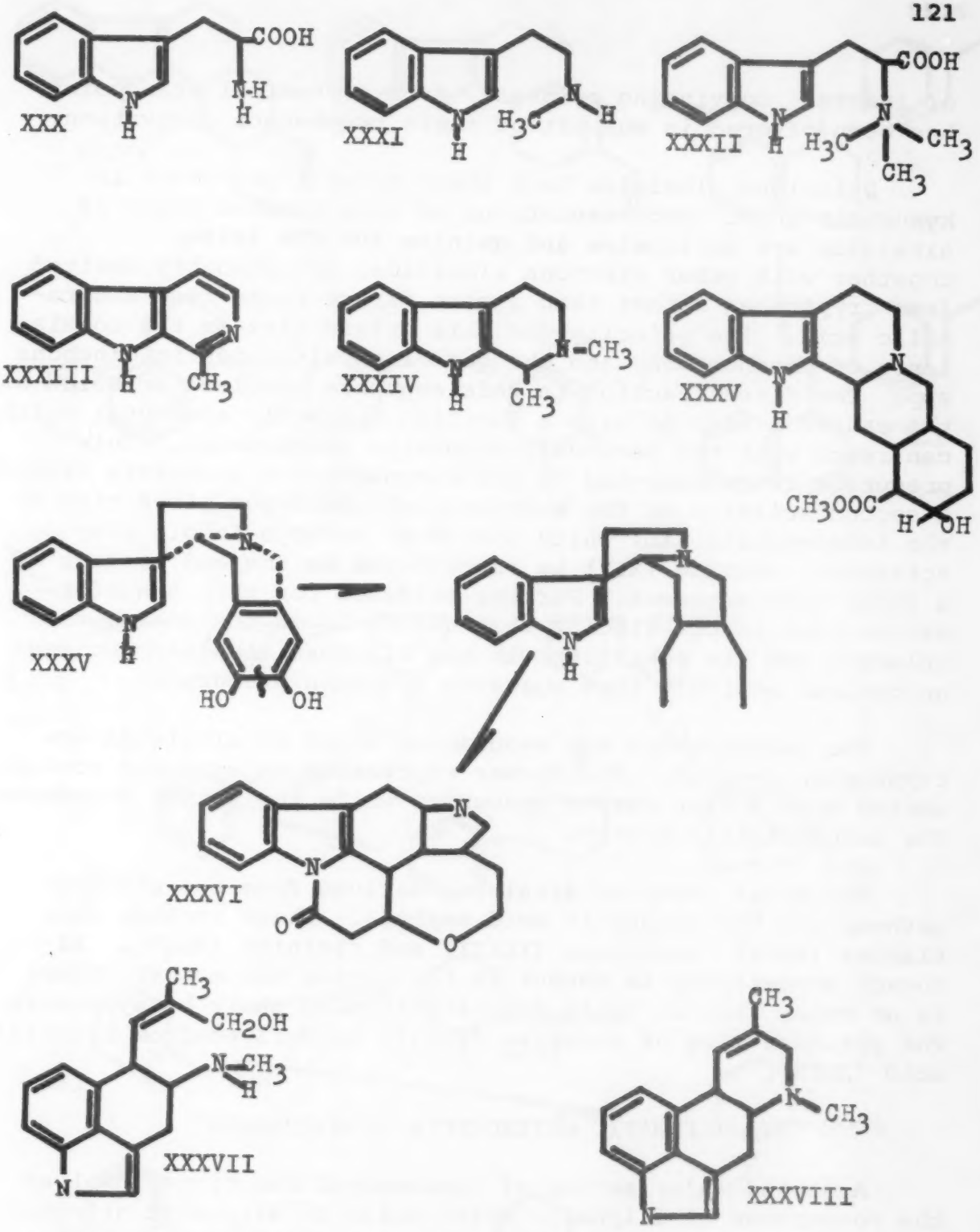


FIGURE 3

of indole. Convincing evidence, from a chemical standpoint, has been offered in support of their prephenate derivation.

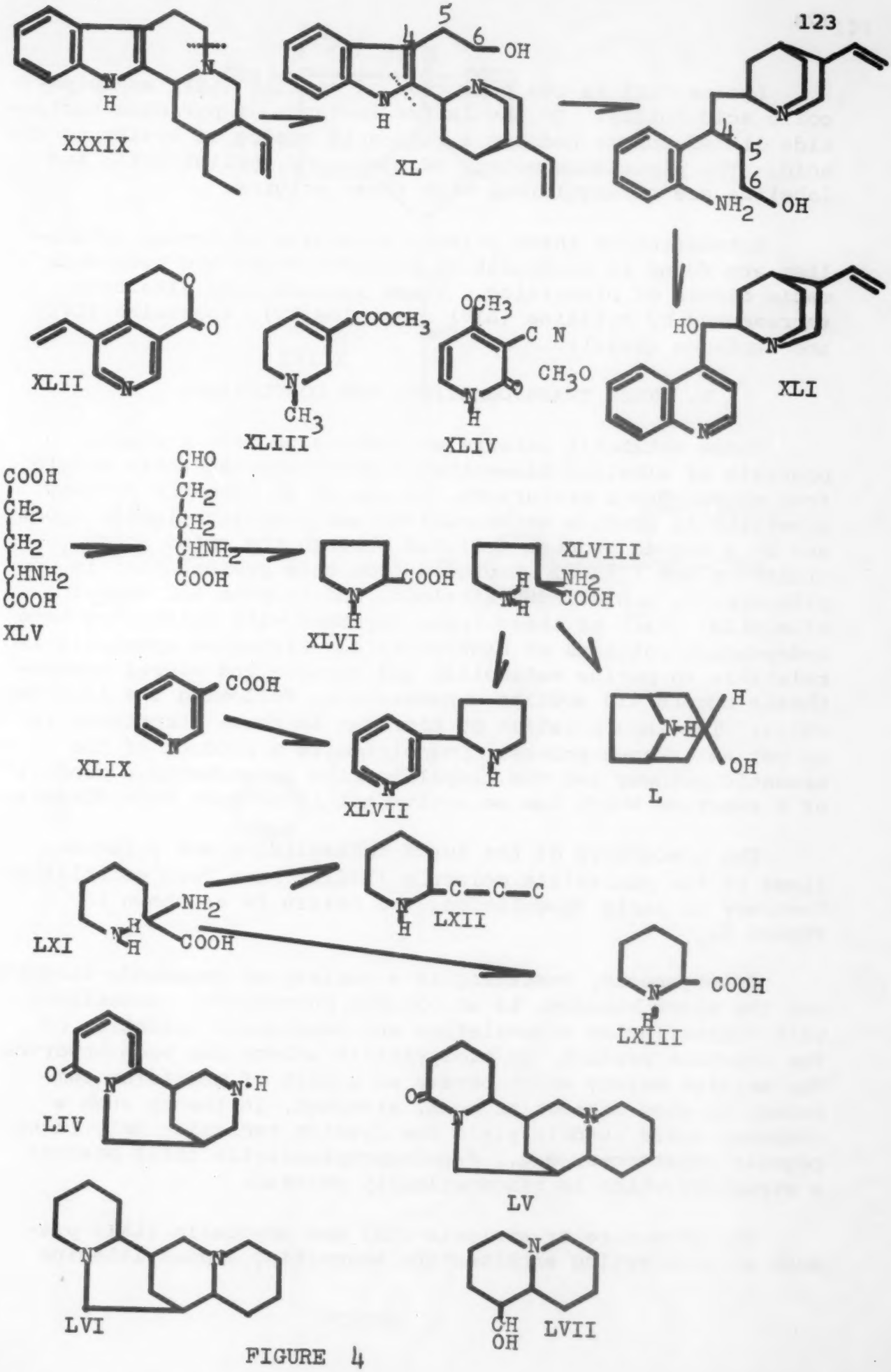
Quinoline alkaloids have their natural precursor in kynurenic acid. Representations of this limited group of alkaloids are dictamnine and quinine and the latter together with other cinchona alkaloids, are probably derived from tryptophan rather than a more direct route from anthranilic acid. The priority for this origin lies in the coexistence of cinchonamine and the quinoline alkaloids in Cinchona spp. The first reaction in this sequence involves scission of the catechol ring to give a function (probably aldehyde) which can react with the secondary aliphatic amino group. This precursor is represented by the corynantheine structure (XXXIV). A second scission of the hypothetical precursor gives rise to the intermediate (XL) which then must undergo indole ring scission. Quinine (XLI) is represented as the end product of a final rearrangement. Further evidence for this transformation lies in the finding that carbon-15 of the yohimbine molecule and its equivalent in the cinchona alkaloids possess an optical activity that suggests a common precursor.

The calycanthine and evodiamine types of alkaloids are tryptophan derived. The former represents an apparent condensation with a four carbon precursor while the latter possesses the anthranillate moiety.

The final group of alkaloids derived from the aromatic pathway are the nicotinic acid analogs. These include gentianine (XLII), arecoline (XLIII) and ricinine (XLIV). Although aromaticity is absent in the latter two member, there is no other logical basis for establishing their biosynthesis. The pyridine ring of nicotine (XLVII) is derived from nicotinic acid (XLIX).

IV. ALIPHATIC HETEROCYCLE BIOSYNTHESIS

A second major series of fundamental reactions involves the conversion of aliphatic amino acids to aliphatic nitrogen heterocycles. The major metabolic pathway to proline (XLVI) is from glutamic acid (XLV); the proline moiety of nicotine (XLVII) and the tropane (L) alkaloids is ornithine (XLVIII) derived. Proof of the biosynthesis has been established in both tobacco and hyoscyamus. The early suggestion that scopolamine originated by a metabolic pathway different from that which produces hyoscyamine is probably not correct.


XXXIX
XL
XLI
XLII
XLIII
XLIV
XLV
XLVI
XLVIII
XLIX
XLVII
L
LXI
LXII
LXIII
LIV
LV
LVI
LVII
FIGURE 4

Lysine (LI) is the precursor of coniine (LII) and pipecolic acid (LIII). In the latter instance, a pyridine-nucleotide linked enzyme reduces a keto-acid analog of lysine to the acid. The piperidine moiety of anabasine, pelletierine and lobeline are cosanguinious with these origins.

Extensions of these primary alkaloids of lysine metabolism are found in condensation products which are hydroaromatic dimers of piperidine. These include type alkaloids represented by cytisine (LIV) anagyrine(LV), sparteine (LVI) and lupinine (LVII).

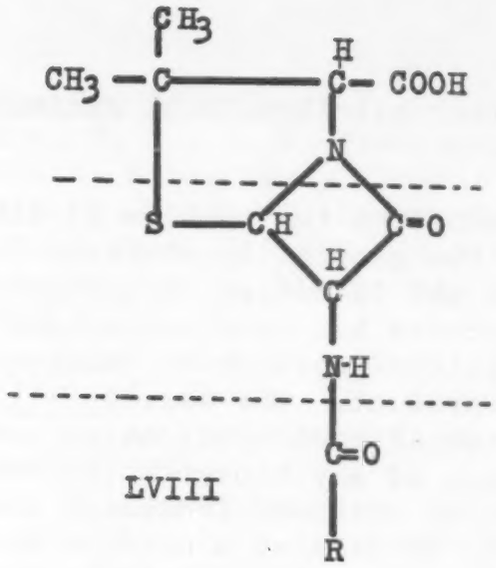
V. OTHER TRANSFORMATIONS AND CONCLUSIONS

These metabolic interrelationships provide a simple protrait of alkaloid biosynthesis which suggest their origin from carbohydrate precursors, by way of an aromatic pathway diverging to produce anthranillate and phenylethylamine types and by a second process mediated through the amino acids ornithine and lysine. Excluded from this presentation is pilocarpine, a histidine alkaloid, and terpene and sterol alkaloids. Each of these types together with colchicine have independent patterns of biosynthesis. Histidine synthesis is relatable to purine catabolism and terpene and sterol biosynthesis occurs via acetate condensation. following the isoprene rules. The incorporation of nitrogen in these structures is as yet an unknown process. Colchicine is a product of the aromatic pathway and the tropolone ring is probably a product of a reaction which has an equivalent in terpene biosynthesis.

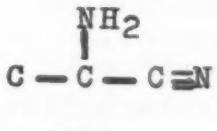
The precursors of the fused thiazolidine and β-lactam rings of the penicillin molecule (LVIII) have been established. Contrary to early speculation, the origin is as shown in Figure 5.

Cyanogenesis, resulting in a variety of compounds throughout the plant kingdom, is an obscure phenomenon. Associated with hydroxylamine accumulation and subsequent oxidation of the reaction product, no biosynthetic scheme has been observed. The amidine moiety which occurs as a part of guanidine compounds is also unknown as such, although, in theory such a compound could readily yield the cyanide radical. Only lathyrogenic substances, e.g., β-aminopropionitrile (LIX) possess a structure which is biogenetically related.

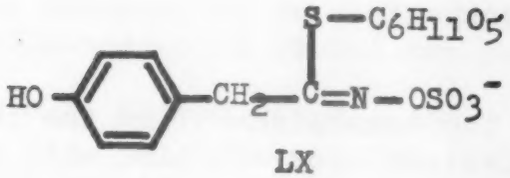
The structure of sinigrin (LX) and amygdalin (LXI) present an interesting architecture suggesting a phenylalanine



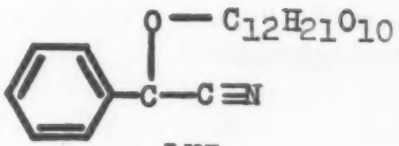
LVIII



LIX



LX



LXI

FIGURE 5

relationship although other nitriles, e.g. ricinine (LII) do not extend this biogenesis.

Experimental approaches to the problem of alkaloid biosynthesis have followed two general approaches; the injection of isotopic tracers, and the injection of unlabeled precursors. In either case, the objective has been to isolate the converted product and in the latter approach to observe increased accumulation of the end product. The use, in vitro of enzyme preparations has had insignificant application and it is essential for confirmation of any biosynthetic reaction. The majority of evidence so far obtained indicates that a given tissue (plant) is capable of forming a product and the data does not imply that the biosynthetic reaction is the mechanism by which the plant produces the end product. The research data thus presents potential capacity rather than absolute biosynthesis. It is apparent that non-alkaloid producing tissue can induce precursor-alkaloid interconversions.

The establishment of the role of metabolic intermediates, in alkaloid biosynthesis, will arrive when plant cells will yield to cultivation practices equivalent to fermentation techniques of yeasts, etc., and when understandings and techniques are obtained for the manipulation of the enzymes of such cells.

REFERENCES

General

(1) Hegnauer, R., Planta Medica 6:1 (1958)
(2) Hughes, G. K., and E. Ritchie, Revs. Pure and Appl. chem. (Australia), 2: No. 3 (1952).
(3) Mothes, K., Die Pharmazie 14:121 (1959); 14:177 (1959).
(4) Robinson, R., "The Structural Relations of Natural Products." Oxford University Press, (1955).
(5) Wenkert, E., Experientia 15:165 (1959).

I. Introduction

(1) Anet, E.F.L.J., G. K. Hughes, and E. Ritchie, Australian J. Sci. Research, A2:616 (1949).
(2) Robinson, R. J., J. Chem Soc., 111:762 (1917).
(3) Robinson, R. J., Nature, 162:524 (1948).
(4) Schopf, C. and H. Bayerle, Ann., 513:190 (1934).

II. One-Carbon Condensation

(1) Byerrum, R. U., J. H. Flockstra, L. J. Dewey and C. D. Ball, J. Biol.Chem., 210:633 (1954).
(2) Byerrum, R. U., L. J. Dewey, R. L. Hamill and C. D. Ball, J. Biol.Chem. 219:345 (1956).
(3) Dubeck, M., and S. Kirckwood, J. Biol.Chem., 199:307 (1952).
(4) James, W. O., and V. S. Butt, Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chemie (7), 182 (1957).
(5) Leete, E., L. Marion and I. D. Spenser, J. Biol. Chem., 214:71 (1955).
(6) Morgan, A., and L. Marion, Canad. J. Chem. 34:1704 (1956).
(7) Scribney, M., and S. Kirkwod, Nature, 171:931 (1953).
(8) Shibata, S., and I. Imaseki, Pharm. Bull. (Japan), 3:277 (1956).
(9) Wiehler, G., and L. Marion, J. Biol. Chem., 231:799 (1958).

III. Aromatization

(1) Battersby, A. R., and B.J.T. Harper, Chem & Ind., 1958, 364.
(2) Dalgliesh, C. E., W. E. Knox, and A. Neuberger, Nature, 168:20 (1951).
(3) Davis, B. D., Advances in Enzymology, 16:247 (1955).
(4) Davis, B. D., Harvey Lecture Ser., 50:230 (1955).
(5) Haase, K. and P. Berg, Naturwiss., 44:584 (1957).
(6) Hahn, G., and F. Rumpf, Ber., 71:2141 (1938).
(7) Hahn, G., and O. Schales, Ber., 68:24 (1935).
(8) Leete, E., Chem. & Ind., 1958, 977.
(9) Leete, E., Chem. & Ind., 1959, 604.
(10) Mann, P.J.G., and W. R. Smithies, Biochem. J. 61:89 (1955) and 61:101 (1955).
(11) Manske, R.H.F. and H. L. Holmes, "The Alkaloids", Vol. IV, Academic Press, New York, 1954.
(12) Mothes, K., F. Weygand, D. Gröger and H. Grisebach, Z. Naturforsch., 13b:41 (1958).
(13) Robinson, R., Nature, 162:524 (1948).
(14) Schöpf, C., and H. Bayerle, Ann., 513:190 (1934).
(15) Späth, E., and F. Kesztler, Ber., 68:1663 (1935).
(16) Sreenivasan, P. R., M. Katagriri and D. B. Sprinson, J. Am. Chem. Soc., 77:4943 (1955).
(17) Suhadolnik, R. J., and R. G. Chenoweth, J. Amer. Chem. Soc., 80:391 (1958).
(18) Suhadolnik, R. J., L. M. Henderson, J. B. Hanson and Y. H. Loo, J. Amer. Chem. Soc., 80:3153 (1958).
(19) Woodward, R. B., Angew. Chem. 68:13 (1956).
(20) Yanofsky, C., Biochim et Biophys. Acta, 16:594 (1955).
(21) Yanofsky, C., Biochim et Biophys. Acta, 20:438 (1956).

IV. Aliphatic Heterocycle Biosynthesis

(1) Abelson, P. H., and H. J. Vogel, J. Biol. Chem., 213:355 (1955).
(2) Lamberts, B. L., and R. U. Byerrum, J. Biol Chem. 233:939 (1958).
(3) Leete, E., L. Marion and J. D. Spenser, Canad.J. Chem., 32:1116 (1954).
(4) Leete, E., and F.H.B. Leitz, Chem. & Ind., 1572, (1957)
(5) Leete, E., J. Amer. Chem. Soc., 80:2161 (1958).
(6) Martin, H. H. and J. W. Foster, J. Bacteriol., 34:167 (1958).
(7) Reinouts van Haga, P., Proefschrift, Delft, 1956.
(8) Reinouts van Haga, P., Biochim. Biophysica Acta, 19:562 (1956).
(9) Vogel, H. J., and D. M. Bonner, Proc. Natl. Acad. Sci. U. S., 40:688 (1954).

V. Conclusions

(1) Arnstein, H.R.V. and P. T. Grant., Bact. Rev., 20:133 (1956).
(2) Ettlinger, M. G., and A. J. Lundeen, J. Amer. Chem. Soc., 78:4172 (1956).
(3) Hegnauer, R., Pharm. Weekblad. 94:248 (1959).

DISCUSSION

Question: Is there evidence that a one carbon unit, such as formate, is involved in alkaloid biosynthesis?

Schwarting: The role of formate has not been established in the biosynthesis of any alkaloid. The role, if it exists, is projected only by those who speculate on biosynthesis patterns.

Ramstad: Some Japanese workers had some evidence for formate induction and/or for methyl group oxidation.

Turner: What is the evidence that scopolamine is the direct precursor of hyoscyamine?

Schwarting: This evidence is not positive, but Reinhouts van Haga has shown that both alkaloids are produced simultaneously. In contradicting the work of Canadian workers who found that labeled ornithine was not transformed to scopolamine, he proposed that results could be explained if one

assumed that scopolamine is the first alkaloid. All other evidence is the reverse of this pattern.

Ramstad: We have had interesting reports from datura grafted on tomato. Introduced hyoscyamine was changed to scopolamine. In this case, the opposite reaction did also occur.

THE BIOSYNTHESIS OF NON-NITROGENOUS DRUGS

H. W. Youngken, Jr.

The purpose of this paper is to review certain highlights of the subject "biosynthesis of non-nitrogenous compounds" as the topic might be of value in the teaching of portions of the general undergraduate course of pharmacognosy. It is not intended that the review deal with the complexities and thorough coverage of step wise reactions concerned in the present knowledge of drug biosynthesis. Further the paper will focus attention largely on the subject as it relates to plant drugs since teachers of pharmacognosy are generally most interested in this area.

It should be stated that the objectives of a biochemical approach along with other methods in the teaching of non-nitrogenous natural drug materials in pharmacognosy is to associate end products of cellular metabolism with the chemistry of the cell or tissues in which they are synthesized. Without this reference the biological and chemical aspects of the subject would seem to be incomplete. Such an association also provides additional background for a better understanding of the biochemical factors of drug usage, a subject of importance in all courses of the pharmaceutical curriculum which deal with drug pharmacodynamics.

The diverse organic products elaborated by cells of living organisms should create a curiosity among students (if the interest is properly cultivated by a teacher) in the manner by which living protoplasm juggles atoms of many molecules so that organic acids, sugars, starches fats, oils, glycosides, steroids and other non-nitrogenous compounds are formed. Whether in the form of crude drugs, mixtures, their extractives or isolated and purified entities, the chemical factors in the origin of the product(s) invite a certain degree of interest.

Partial answers to some of the chemical problems in the biosynthesis of non-nitrogenous drugs, such as contain or represent any of the above groups, are known. On the other hand, for most the complete knowledge is still to be gained; indeed, in several instances even partial metabolic pathways of biosynthesis are still unknown. The same may be said for nitrogenous drugs.

Thus the teacher must be careful in the manner by which this rather speculative subject is presented since the evidence

for a complete biosynthesis based upon research is frequently fragmentary or incomplete. On the other hand, whether complete or incomplete this approach has value at least in bringing together some of the major concepts of the cell as a chemical factory. Furthermore, much progress in the knowledge of biosynthetic pathways is being made.

Among drug plant products belonging to the non-nitrogenous class are those produced by artificial fermentation, i.e. alcohol, the organic acids (acetic, citric, tartaric etc.) and by natural processes, i.e. sugars, complex carbohydrates (including gums and mucilages), fatty acids or lipids, volatile oils, certain flavones, steroids, etc.

In teaching the subject matter concerned with the biosynthesis of any of the above compounds it should be recognized that all major chemical mechanisms of the plant are closely integrated. One can not be considered more important than another. In fact from the point of cellular kinetics changes in the cellular synthesis of one compound may very well result in changes in others. Also, prior to presenting these topics to students one should make certain that the basic reactions as occur in the processes of photosynthesis and respiration are understood.

Photosynthesis and Respiration: Since photosynthesis is the specific biosynthetic process responsible for the primary transformation of inorganic CO_2 and H_2O into organic compounds and since this process is the ultimate source of all organic drugs it should be reviewed early during the general course. The two fundamental series of reactions in photosynthesis, namely (1) absorption of light followed by light-energized decomposition of water and (2) the transformation of CO_2 into sugars such as by the Robin Hill reactions, require careful explanation for the proper understanding of the origin of other biochemical "building blocks" which follow.

The process of cellular respiration (in many respects the reverse of photosynthesis) should also be reviewed since during respiration cellular compounds are broken down and when complete the process provides CO_2, H_2O and energy for other specific cellular reactions. The oxidative enzymes that are involved in the cellular respiratory processes are of importance in the understanding of the metabolic cycles.*

*For example those of Krebs, Thunberg, etc. (For a review of plant respiration see James, W.O.; Endeavour 13: 155-162, 1954).

Most of the study of photosynthesis and respiration comes in basic biology or biochemistry. However, it is often our experience to find that further review early in pharmacognosy is of great benefit to students. This can be said especially for the referral to organized pathways for organic acid synthesis, i.e. the citric acid, tricarboxylic acid cycles, etc. These are important phases of the respiratory process and can be regarded as "blue prints" which show relationships of various compounds in cellular metabolism. A mastery of certain metabolic cycles such as these* may contribute significantly to a better understanding of steps in the biosynthesis of pharmaceutical substances. Generally metabolic cycles are introduced in the modern course of biochemistry which in the newer curriculums of the colleges of pharmacy often comes concurrently with pharmacognosy. However, the metabolic schemes presented in such introductory courses are usually limited due to time.

Some of the highlights of the material dealing with the teaching of biosynthesis of certain non-nitrogenous compounds in pharmacognosy are as follows:**

Organic acids: A number of organic acids make up the constituents of natural drug products. A very few are dealt with per se as "drugs" in pharmacognosy. Examples of these are citric and tartaric acids which can be biosynthesized by various fermentation processes. Although rich in citric acid the citrus fruits are not as frequent sources for this acid as are strains of Aspergillus niger or the domestic production from sucrose or other carbohydrates.

The use of fermented grape tissues, Vitis vinifera, for the production of tartaric acid is described in pharmacognosy and other texts.

Since so many raw drugs in pharmacognosy contain non-nitrogenous organic acids, or these are involved with the metabolic cycles in the step wise synthesis or degradation of other raw drug constituents, the general successive steps

*The need for this approach in teaching pharmacognosy has been outlined previously by the author. (1)

**The author has employed much material for the discussion which follows from the pages of Pharmacognosy, Chapter 2, 2nd Ed. by Pratt, R. and Youngken, H. W., Jr., J. B. Lippincott Co., Phila., Pa., 1956.

of plant acid formation from plant sugars should be presented. This process deals with three major steps of cellular respiration: (1) the conversion of hexose sugars to pyruvic acid (a process called glycolysis) and (2) the oxidative degradation of pyruvic acid through a number of organic acids and enzymatic catalyzed reactions to CO_2 and water, and (3) the so called pentose shunt from which such 5 carbon sugars as ribose, ribulose, xylose, etc. as well as the 7 carbon sugar sedoheptulose sugars are derived. Glycolysis, as is known, is the first step of both aerobic respiration and anaerobic fermentation. The oxidation of pyruvic acid to CO_2 and water is strictly aerobic.

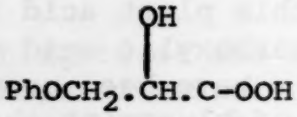
Like many biological processes, the oxidation of pyruvic acid is cyclic. This phase of the respiratory process is called the Krebs cycle (in honor of the biochemist who first elucidated the pathway of oxidation) or the citric acid cycle (because of the role of this plant acid in the process). It is also known as the tricarboxylic acid cycle. Many modifications of the Krebs cycle have been proposed, but the scheme may be considered a kind of blueprint that shows the relationships of the various components involved in the terminal phases of respiration. It also points the way toward the possible initial steps in many processes involved in the biosynthesis of pharmaceutically and medicinally important substances.

The first step, immediately preceding the Krebs cycle is degradation of pyruvic acid (CH_3--CO--COOH) to yield carbon dioxide and a 2-carbon fragment. This 2-carbon derivative then condenses with the 4-carbon dicarboxylic acid (oxaloacetic) to yield the 6-carbon (tricarboxylic) citric acid. Then by successive steps, passing through each of the plant acids, a molecule of oxaloacetic acid is regenerated and becomes available for condensation with another 2-carbon derivative of pyruvic acid, and the cycle is repeated.

Other non-nitrogenous organic acids dealt with as constituents of drugs in pharmacognosy are the several aromatic acids i.e. benzoic and cinnamic acids in balsams, phenolic acids in tannins and resins, etc. The biosynthesis of most is as yet obscure. On the other hand much evidence can be found from studies with micro-organisms and fungi which link biosynthesis of the above compounds and other cellular aromatic acids with the pentose shunt. For example by an initial cleavage at the α-carbon of phenylalanine, phenols may be formed. Or by an initial oxidation of phenylpyruvic acid and/or phenylalanine benzoic and cinnamic acids are said to be biosynthesized.

Carbohydrates: The literature is extensive with evidence for biosynthetic reactions for simple carbohydrates. Some concepts are plausible, although not complete, for the biosynthesis of more complex carbohydrates, such as the gums, mucilages, pectins, etc. The knowledge of the synthesis of starch and sugars via the photosynthetic process is extensive and this is a common subject for discussion in pharmacognosy.

By use of carbon dioxide containing radioactive carbon (atomic weight 14) and by allowing plants a very short photosynthetic period, it is possible to determine some of the intermediate products along the pathway from carbon dioxide to sugars. The first stable intermediate product determined by this method is 3-phosphoglyceric acid, and the radioactive carbon appears first in the terminal (COOH) position of the acids, as follows:



About 70 per cent of the carbon fixed by the plant can be recovered in this form following 5 seconds of photosynthesis with the tagged CO_2. Following longer periods of exposure to light, the radioactive carbon begins to appear in the remaining two carbon atoms of the phosphoglyceric acid. These facts suggest that one of the early steps in the transformation of carbon dioxide is attachment to a pre-existing 2-carbon compound which itself is derived from carbon dioxide. The pathway by which this 2-carbon compound is formed is not known, but it is believed that it is a cyclical process in which some of the compound is shunted out of the cycle in the formation of sugars while some is regenerated and then enters the cycle again. The coupling of two triose phosphate units, derived from phosphoglyceric acid, could produce glucose- and fructose-6- phosphates, both of which, along with glucose-1-phosphate, accumulate in high concentrations during short periods of photosynthesis. From these compounds, possessing the 6-carbon skeleton characteristic of the major sugars, the plant produces glucose and fructose.

The biosynthesis of starch and cellulose as polymerization products of glucose units and the derived carbohydrates from glucose, arabinose, xylose, glucuronic or galacturonic units are steps worth demonstrating for the subject of carbohydrate biosynthesis. The extent of the material depends upon the student's background in introductory biochemistry.

Lipids: Most of the present knowledge of the biosynthesis of fatty acids and lipid formation in nature has been obtained from studies of micro-organisms and animal tissues. However, the same principles may apply to the biosynthesis of these materials which constitute important components of higher plant drugs, namely their synthesis by increments of 2-carbon fragments.

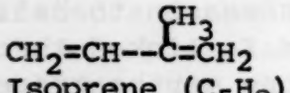
The biosynthesis of lipids, unlike that of sugars, is not limited to the green leafy portions of the plant whence translocation to other organs occurs: the lipids are synthesized in the seeds and fruits themselves, as well as in other tissues. Further, the lipids are synthesized from some precursor, possibly a carbohydrate, that is rich in oxygen. The results of research have also suggested, as would seem probable on theoretical grounds, that free fatty acids are formed first and then, as the fruit or seed matures, are esterified to form components which constitute the complex mixtures that are known as oils, fats, and waxes.

It will be recalled that in the respiration of sugars, following glycolytic degradation of hexoses to pyruvic acid, the pyruvic acid itself gives rise to a 2-carbon fragment which is swept up into the Krebs cycle. This same 2-carbon fragment is formed also when fatty acids undergo biological oxidation, and it seems likely that the Krebs cycle or another cycle functions also in the terminal phases of the oxidation of lipids. Of even greater significance from the standpoint of the biosynthesis of lipids is the fact that this 2-carbon fragment may be acetylphosphate, (CH_3--O--O—pH). There is evidence that acetyl phosphate is involved in the biosynthesis of fatty acids. Thus there is reason to believe that the metabolism of sugars and lipids is linked through an intermediate which they share and that one may be transformed into the other in the living cell.

There is still further evidence of the interrelationship of photosynthesis and its resultant carbohydrates, on the one hand, and of lipids, on the other hand, in the living chlorophyll-bearing plant. Cytochemical studies with refined technics reveal coronae of fat droplets surrounding the chloroplasts and leucoplasts, suggesting that synthesis of fatty substances may occur within the plastids.(2) Furthermore, experiments with isotopic carbon dioxide have shown that the tagged carbon appears in lipids within 5 minutes after exposure of dark-adapted plants to light.

In bacteria and in mammals fatty acid biosynthesis involves a precursor which is common also to carbohydrate metabolism. In the living cell this precursor probably is an acetic acid derivative, very likely acetylphosphate as previously mentioned. When the organisms are supplied with acetate or acetic acid with the carboxyl carbon isotopically tagged, the isotopic carbon soon appears in the fatty acids of the bacteria and in the fatty acids of the liver and the fat depots of animals. The isotopic carbon always appears in the position of the carboxyl carbon atoms and of every second carbon atom of the chain. The supposition is that 2 molecules of acetic acid condense to form acetoacetate, which then is reduced at the carbonyl group to yield the 4-carbon-atom chain of butyric acid. Condensation of the butyric acid with another molecule of acetate and similar reduction of the carbonyl group would yield the 6-carbon-atom chain of caproic acid. By successive repetitions of the process, one more molecule of acetate being added to the product at each step, a whole series of saturated fatty acids, each one containing 2 more carbon atoms than its predecessor in the carbon chain, could be built up. In the living cell, acetate is converted to the higher fatty acids only when ATP or some other suitable source of high-energy phosphate is available, but acetylphosphate is readily utilized. It seems probable that acetylphosphate (commonly called coenzyme A) is the key compound in the reaction of nature.*

Volatile Oil Terpenes: Fundamentally most volatile oils, certainly not all, are isoprenoid compounds--they are formed through fusion of isoprene units.** Isoprene is a 5-carbon compound with the following structure:



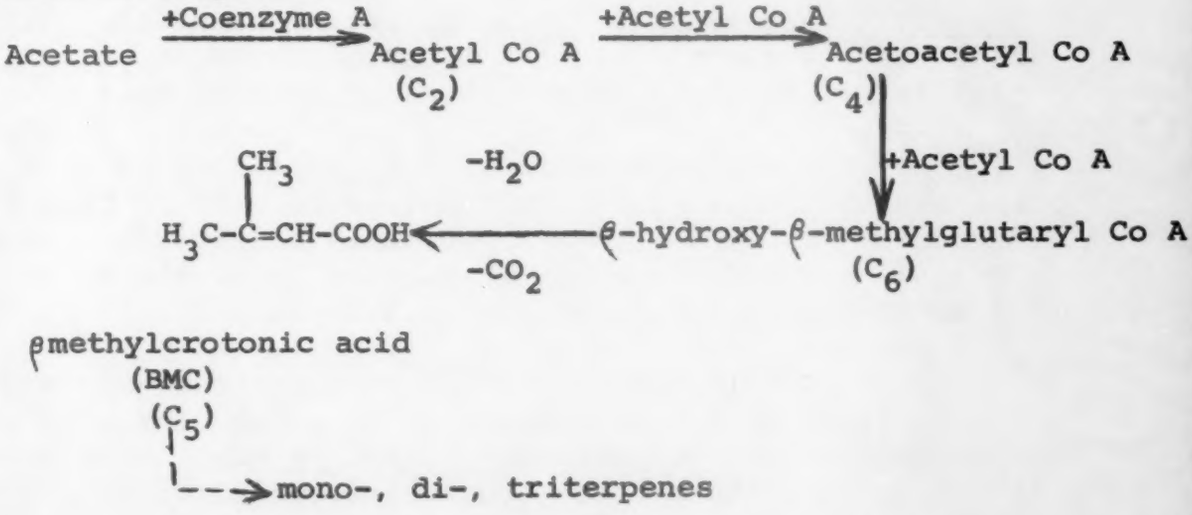
Isoprene (C_5H_8)

*The acetyl group in association with coenzyme A is also referred to as "active acetyl" or "active acetate". For other pathways which may be involved in the building up of fatty acid molecules see Castelfranco, P., et al: Fat metabolism in higher plants, J. Biol. Chem 214: 567-577, 1955.

**Exceptions are volatile oil of mustard (allylisothiocyanate), organic sulfides and mercaptans, various indole derivatives, etc.

The volatile oils are formed by condensation of 2, 3, or 4 of the elementary isoprene units which yield, respectively, the monoterpene, sesquiterpene or diterpene oils. Thus, the skeletal structures of monoterpene oils contain 10 carbon atoms; those of sesquiterpenes, 15; and those of diterpenes, 20. In the simplest monoterpenes, 2 isoprene units are linked together to form an open chain, such as in myrcene (the active constituent of myrica oil, or oil of bay, obtained from Pimenta racemosa) and its derivatives such as geraniol and citronellol (present in the rose and in certain grasses): or 2 isoprene units may be linked into a 6-membered ring as in limonene, the major constituent of some of the oils of citrus fruits. From these basic structures many modifications may be made: even the simplest volatile oil usually contains many individual constituents.

Although much has been postulated concerning the biosynthesis of terpenes, comparatively little is known about the formation of most of them in the living plant. However, there is experimental evidence that the 5-carbon acid, 3-methylcrotonic acid (BMC), which is found in many plants may be an important intermediate in the biosynthesis of terpenes.(3) The following scheme seems to be a reasonable pathway to assume for the first stage (up to formation of BMC) in the elaboration of terpenes:



Sterols: It has been said that sterols are present in every plant or animal cell save those of bacteria, and recent research indicates that they may occur in at least some species of bacteria. The universal distribution of sterols in nature may be a mere coincidence without deeper significance, but this seems unlikely. Their widespread occurrence would seem to indicate some fundamental significance in cellular metabolism.

However, although important functions of sterols in animal physiology are known, the significance of these compounds in the economy of the plant remains obscure. Equally obscure is the pathway of their biosynthesis. However, the fragmentary evidence that is available points to two general conclusions: (1) that acetyl coenzyme A, which participates in the biogenesis of organic acids, terpenes and carotenoids, may also be an intermediate in steroid biosynthesis; and (2) that 3- and 5-carbon units (such as isoprene) may also be involved in biosynthesis of steroids, such as cholesterol in animal tissues.* However, formation of steroids probably does not directly involve pyruvic acid and the Krebs cycle. Indeed, pyruvic acid may decrease synthesis of steroids such as cholesterol. The suggestion that a 3-carbon unit is involved in steroid formation is based on the observation that the isopropyl moiety of isovaleric acid is a precursor for cholesterol synthesis in the rat, independently of the 2-carbon acetate intermediate. Further evidence is the fact that in other animal tissues, squalene (a 5-carbon isoprene) can be converted into cholesterol without the intermediate formation of 2-carbon units.

In work with plants, it has been shown that the isotopic carbon from acetate tagged in the carboxy group is not significantly incorporated into the steroid digitalis glycosides of Digitalis purpurea.(4) This supports the thesis that steroid biosynthesis can by-pass the 2-carbon fragment which is essential in natural synthesis of many other important compounds.

Glycoside biosynthesis in Digitalis is increased when the plants are provided with cholesterol.(5) Although the mechanism involved is not known, this observation suggests possible leads for further investigation of the biosynthesis of complex steroid structures in plants.

Much work is necessary before we can conclude much of significance as to the pathway(s) by which Digitalis steroid glycosides are biosynthesized. Work in our laboratories indicates somewhat that these drug plant constituents are formed in largest amounts during active metabolism--that involving

*For an explanation of the building up of large organic structures such as steroids from acetyl coenzyme A and other small carbon fragments see standard works in biochemistry, such as Fruton, J. S., and Simmonds, S.: General Biochemistry, New York, Wiley, 2nd Ed. (1958).

carbohydrate, fatty acid and sterol synthesis. Although from plant feeding experiments C^{14} labeled acetate was not utilized in the sterol glycoside synthesis of Digitalis, as it has been demonstrated by Little and Block (6), Block and Rittenberg (7) for animal tissues and Sonderhoff et al.(8) and others for ergosterol synthesis in yeast and neurospora, other carbon intermediates should be investigated in this work. Among these attention should be directed to the direct pathway from 3 or more carbon intermediates such as acetoacetic acid, isovaleric acid and/or the isoprenoids.

Conclusions:

It seems reasonable to assume that non-nitrogenous and nitrogenous drug plant constituents should be regarded by students as products of an orderly biosynthetic process. This approach in the teaching is a basic one and serves to tie together the biological chemistry with the applied biology and chemistry which are presented in the course. It is a subject that not only can stimulate students but also a teacher. Therefore to some extent both well established and hypothetical schemes of the in vivo synthesis of drug constituents should, we believe, be included in the general undergraduate course of pharmacognosy.

REFERENCES

(1) Youngken, H. W., Jr. An organized approach to the study of natural products through the fundamental consideration of cellular biosynthetic and structural processes. Teachers' Seminar on Pharmacognosy and Related Subjects. University of Utah College of Pharmacy, Salt Lake City, August 10-14,1953.

(2) Scott, F.M. The distribution and physical appearance of fats in living cells - introductory survey, Am. J. Bot. 42: 475-480 (1955).

(3) Johnston, J.A. et al. The metabolism of isoprenoid precursors in the plant system. Proc. Nat. Acad. Sci. U.S.40: 1031-1037 (1954).

(4) Djao, E.H. and Youngken, H.W.,Jr. A study of carbon^{14} labeled acetate in Digitalis purpurea glycoside biosynthesis. J. A. Ph. A. Sci. Ed. 44: 321-325 (1955).

(5) Tsao, D.P.N. and Youngken, H.W.Jr. The effects of cobalt, acetate, ascorbic acid and cholesterol on growth and glycoside biosynthesis in Digitalis purpurea.J. A. Ph. A. Sci. Ed. 41: 407-414 (1952).

(6) Little, H.M. and Block, K. Studies on the utilization of acetic acid for the biological synthesis of cholesterol. J. Biol. Chem. 183: 33 (1950).
(7) Rittenberg, D. and Block, K. The utilization of acetic acid for the synthesis of fatty acids. J. Biol. Chem. 160: 417-424 (1945).
(8) Sonderhoff, R.V. and Thomas, H. Die enzymatische dehydrierung der trideutero-essigsaure. Ann. Chem. 530: 195 (1937).

DISCUSSION

Dunn: You spoke about pathways in the synthesis of volatile oils, etc. Is there any reason why these reactions go in the particular direction they do?

Youngken: The physical biochemist can plot mathematically according to kinetics or enzyme energy reactions the way they go. These mathematical calculations indicate the energy levels and bear out the results obtained with the accumulation of product of series reactions.

Albers: In talking to undergraduate students about the citric acid cycle--where does the oxaloacetic acid come from?

Youngken: It comes from the two-carbon fragment--active acetate.

Kellerman: Most of it comes from fixation of CO_2 by pyruvic acid. There are 3-4 methods of CO_2 fixations to get them down to the organic compounds that might reach pyruvic acid.

Redman: I'd like to ask if undergraduate students are expected to explain the biosynthesis of all of the acitve plant constituents that are included in the book?

Schwarting: I don't see the reason to expect them to know all of these.

Youngken: I like to get in a little of it where we can, but don't make a major issue of it in the undergraduate course.

ADVANCES IN NATURAL PRODUCTS CHEMISTRY

Lloyd M. Parks.

In a paper of this title a choice must be made among the many topics that might be included. With the emphasis in modern pharmacognosy shifting away from the more classical approach, such topics as biogenesis and biosynthesis of plant constituents and the use of radioactive tracer techniques might well be included. In the areas of isolation, separation and analysis of plant constituents one might also include such topics as fermentation techniques, chromatography, electrophoresis, and instrumentation techniques.

Before preparing this paper, however, I studied the program for this Seminar and noted that each of these mentioned topics is being covered specifically by others, some of whom have preceded me and most of whom are to follow me on the program. Instead of duplicating what may be covered by others and instead of attempting to give an exhaustive survey of the many advances in natural products chemistry in the brief time alloted, I have chosen to attempt to cover in some little detail only a few recent advances that are concerned chiefly with the structure determination of natural products as well as with their synthesis.

In doing so it is my intention to give you some appreciation for the significance of these advances which are being utilized with increasing frequency in the study of natural products and the applications of which are now becoming commonplace in the literature dealing with natural products chemistry.

The development and application of physical methods and of chemical physics perhaps has had greater impact, not only on natural products chemistry but also on organic chemistry in general, in the past few years than any other single development. The use of ultraviolet spectra, infrared measurements and X-ray diffraction has become standard operating procedure in the study of natural products. These tools, along with the techniques of optical rotatory dispersion, nuclear magnetic resonance, and the principles of conformational analysis, the latter made possible by the revelations of chemical physics, have permitted new methods of approach to the stereochemical configuration of organic molecules.

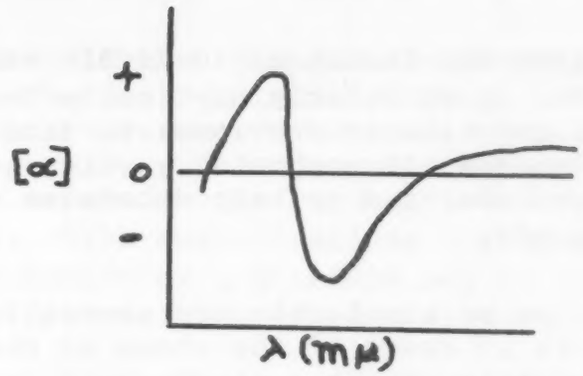
They have enabled the chemist to unravel the molecular architecture of some of the most complicated natural products and to confirm their conclusions by total synthesis of the same compounds. The chemist is now able to define the molecule of a natural principle exactly in terms of its constitution, its configuration, and its conformation. By constitution is meant the number and type of atoms present and the way in which they are joined together. By configuration is meant the relative order in which the covalent bonds of the molecule are directed with respect to each other in space. And by conformation is meant the preferred arrangement of all the atoms in the molecule in space when allowance has been made for the interplay of non-bonded interactions.

This paper will be concerned with two recent advances, the technique of optical rotatory dispersion and the principles and applications of conformational analysis.

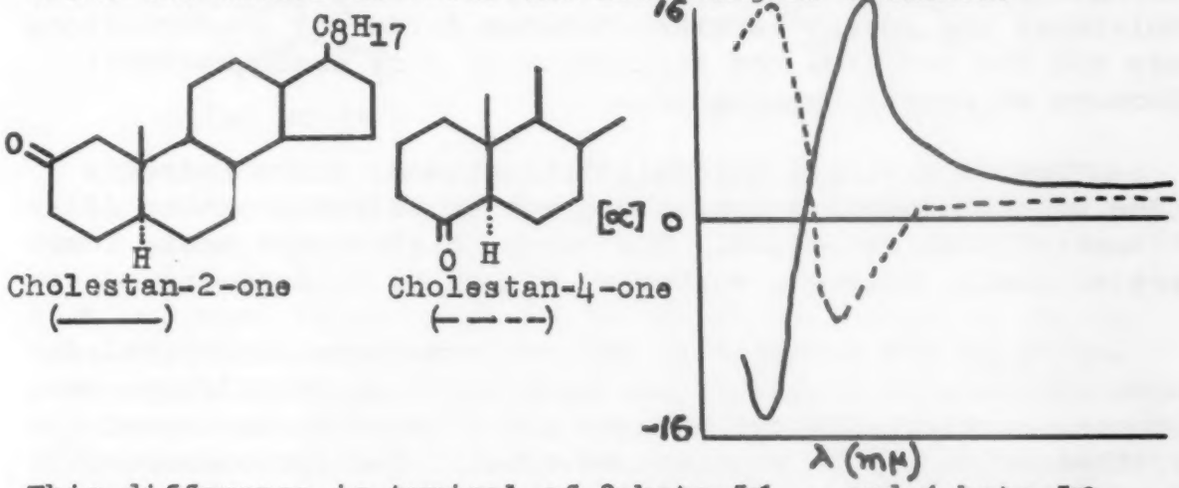
Rotatory dispersion represents the measurement of optical rotation at different wave lengths which as such is not new. Some such measurements were made in the early 19th century but, until a few years ago, the phenomenon had been studied chiefly by physical chemists and not by organic chemists as a technique for solving structural problems.

Optical rotation is usually measured at the sodium D line of the spectrum, but rotations in the ultraviolet region are as much as 10 to 100 times larger. This technique has been developed by Djerassi and his coworkers at Wayne State University who, with the use of a spectropolarimeter which will measure optical rotations at different wave lengths, have made measurements of more than 1000 dispersion curves in recent years. Since the work involves micro technique, it is of significance in natural products where frequently only small amounts of the compounds are available.

To obtain a dispersion curve on a compound, rotation has to be measured through its absorption band which in most organic compounds lies in the U. V. region. The light absorption must also be low and the absorption maximum must occur in an accessible region of the spectrum. The carbonyl group is an example, since it absorbs in the 270-300 mμ region. When in an asymmetric environment the carbonly group shows an unequal absorption of right and left circularly polarized light (Cotton effect). This results in a curve with peaks and troughs:

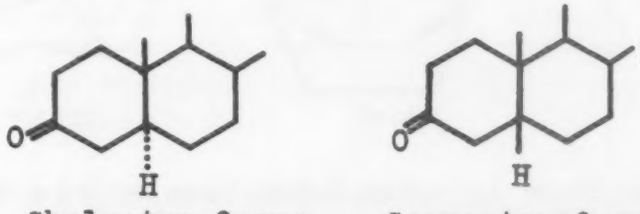


Since a steroid molecule is built around a chain of asymmetric carbons, a carbonyl group is at most only one atom away from an asymmetric center. This changes the valence angle and distorts the asymmetric system, which distortion is reflected in rotatory dispersion changes. Thus with cholestan-2-one and cholestan-4-one the following is obtained:



This difference is typical of 2-keto-5α - and 4-keto-5α - steroids respectively and a differentiation between these two types could not be accomplished by any other tool.

An example of the sensitivity of the method to stereochemical differences is illustrated with cholestan-3-one (trans) and coprostan-3-one (cis).



Cholestan-3-one Coprostan-3-one

which differ only in the nature of the A/B ring juncture and show differences in dispersion curves. This difference also is typical of 3-keto-5α - and 3-keto-5β - steroids, irrespective of the nature of the angular substituent (CH_3 or H).

Djerassi has used the technique to locate carbonyl groups in polycyclic systems (particularly applicable to steroids); to solve analytical and kinetic problems; to find small differences in conformation and stereochemistry which cannot be detected by other methods; and to help determine absolute configuration in compounds.

The conformations of a molecule are generally regarded as those arrangements in space of the atoms of the molecule that can arise by rotation about a single bond and that are capable of finite existence. In a DL pair of optical isomers, for example, there can be only one configuration of each member but there may be many conformations of each. Almost all molecules have theoretically an infinite number of conformations. In general, however, only a few of the possible conformations are energetically preferred. For the majority of molecules the energy barriers between different conformations are too low to allow the separation of pure conformational isomers at normal temperatures.

Thus in a simple molecule like ethane, since there is free rotation about a bond there are an infinite number of "isomers" that can exist. The energy differences among them are so small, however, that they cannot be separated.

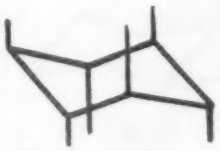
Much of the interest in the conformational analysis of natural products chemistry has been with regard to ring compounds, particularly cyclohexane and polycyclic saturated systems which may be regarded as substituted cyclohexanes. Here we find a more fixed conformation because of the ring. Cyclohexane can exist in only two conformations free from angle strain, i.e., either the boat form or the chair form, the latter of which is more stable as borne out by physical evidence. And derivatives of cyclohexane tend to take the chair form whenever this is stereochemically possible:

Boat Chair

The boat form is considered less stable because the two hydrogens designated are very close together and a "non-bonded interaction" is present, i.e., these groups repel each other. The interaction energy between two non-bonded atoms is weakly attractive up to distances of approximately the sum of the Van der Waals radii of the atoms concerned. (Van der Waals

radius is one-half that distance at which attractive forces between atoms become repulsive forces). At distances less than this the interaction energy becomes repulsive. In general the energy of a particular conformation of a molecule depends on the presence or absence of repulsive interactions between non-bonded atoms. With qualifications for other forces, the most stable conformation of a molecule may be selected by the principle of the minimization of repulsive non-bonded interactions.

Two types of bonds are present in the cyclohexane molecule: axial bonds which are perpendicular to and above or below the plane of the ring (are parallel to the threefold symmetry axis of the ring) and equatorial bonds which are in the plane of the ring (radiate out from the ring):

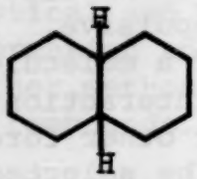


Axial bonds

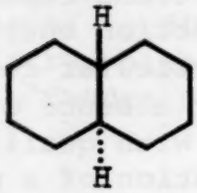
Equatorial bonds

Scale models of the cyclohexane molecule show that the axial bonds alternately point in opposite directions (up and down) with respect to the plane of the ring as do also the equatorial bonds. They also show that any substituent larger than hydrogen in an axial conformation is closer to the two axial hydrogen atoms on the same side of the ring than the same substituent in an equatorial conformation is to the adjacent equatorial and axial hydrogen atoms. Thus the stronger (repulsive) 1:3 interactions dominate the energy relations and, in general, a substituent prefers to adopt an equatorial rather than an axial conformation. To put it another way, equatorial substituents (in the plane of the ring) are usually not hindered by other substituents in the same ring (because they are farther away and more free to rotate) while axial substituents (above or below the plane of the ring) are subject to steric hindrance from other substituents (because they are closer together and not free to rotate). Thus at a given position in a cyclohexane ring system a substituent larger than hydrogen is more stable in an equatorial than in an axial conformation.

Proceeding to bicyclic systems, one of the simplest is the decalins which may be regarded as two fused cyclohexane rings. These rings may be fused in such a way that the two hydrogens at the ring juncture are either cis or trans in their relation to each other.

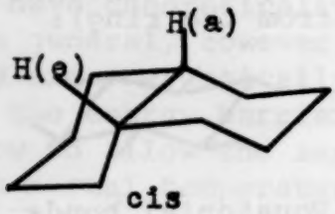


cis decalin

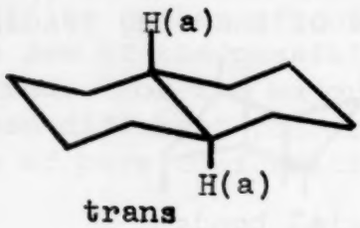


trans decalin

This type of representation does not give an accurate picture of the shape of the molecule. When they are shown in conformational drawings



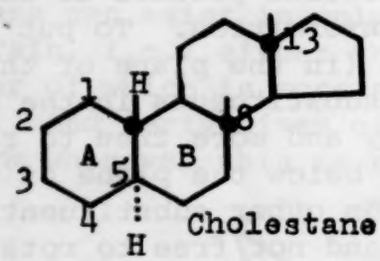
cis



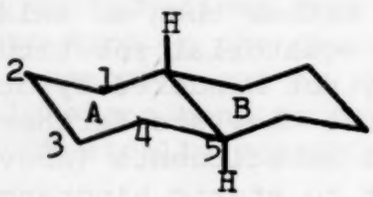
trans

it may be seen that trans decalin is a flat, linear type of molecule while cis decalin is not flat.

Going on to a polycyclic system as in the steroids, in a ring system of the cholestane type the hydrogens at the junction of rings A and B must be axial (1, 2 trans, analogous to trans decalin) while in a ring system of the coprostane type the hydrogens at the junction of rings A and B must be axial-equatorial (1, 2 cis, analogous to cis decalin)



Cholestane



In the cholestane type, therefore, the β configurations (above the plane of the ring) at positions 2 and 4 must be axial and the α configurations (below the plane of the ring) at positions 1 and 3 must be axial (because the axial bonds alternately are above and below the plane of the ring). By the same reasoning the α configurations at positions 2 and 4 must be equatorial and the β configurations at positions 1 and 3 must be equatorial. In this way the configurations and conformations of all positions in ring A of the molecule can be deduced. In

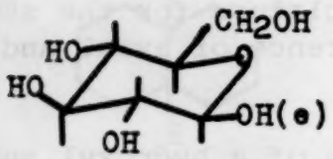
the same way the β configurations at positions 8 and 13 are deduced to be axial. This also serves to illustrate the relationship between the α and β nomenclature for the steroids introduced by Fieser and the occurrence of axial and equatorial bonds.

To determine the configuration of a hydroxyl substituent in the 3-position of the cholestane system, such as 3-cholestanol for example, it can be oxidized to the ketone and the ketone reduced with sodium and alcohol or with lithium aluminum hydride, either of which will give the more stable product which would be β (equatorial) in this case. If the product of this reaction sequence is identical with the starting product then the original compound is a 3β-cholestanol. If it is different (an epimer) then the original compound must be a 3α-cholestanol. Assignment of configurations at different positions in the steroid nucleus have been accomplished on the basis of data of a similar type.

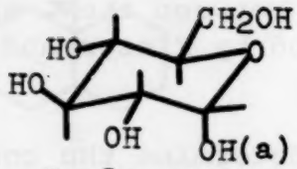
The physical and chemical properties of a molecule are related to its preferred conformation. Some common examples include specific absorption in the ultraviolet and infrared regions; reaction rates in the hydrolysis of esters, esterification of alcohols, oxidation of alcohols, reduction of ketones, etc.; and the relative stabilities of epimers. By use of information of this type, which can be obtained experimentally, it is also possible to determine the preferred conformation in many positions of the molecule.

The applications of the principles of conformational analysis are numerous and varied. It makes possible a rational explanation of many phenomena which have been observed with natural products, as well as an interpretation of physical and chemical properties and reactions of natural products which have been recorded in the earlier literature. By application of conformational analysis it is possible to represent correctly the complete stereochemical structures of natural products as well as to accomplish their complete stereospecific synthesis. A few examples will suffice for illustration.

The equilibrium mixture of glucose after mutarotation has a rotation, $[\alpha]^D = +52.3$ representing 63% β-D-glucopyranose, $[\alpha]^D = +20.5°$, and 37% α-D-glucopyranose, $[\alpha]^D = +109.6°$, indicating that the β-anomer is the more stable. This is consistent with their conformational structures showing all OH groups in the β-anomer to be equatorial while one of the OH groups in the α-anomer is axial.

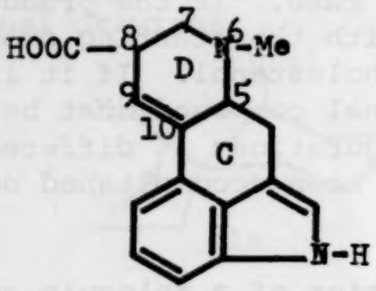


-D-glucopyranose

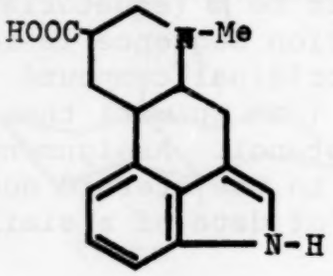


-D-glucopyranose

In working out the structure of the lysergic acid part of the ergot alkaloids four stereoisomeric dihydrolysergic acids were obtained upon hydrogenation of lysergic acid

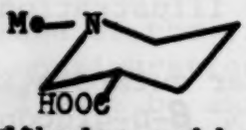


Lysergic Acid



Dihydrolysergic Acid

with dihydrolysergic acid-I as the main product. Since it is the most stable it may be assigned the conformation shown below, with all substituents on the piperdine ring equatorial. Its 8-epimer, dihydroisolysergic acid-I, must then be represented as shown, with the COOH axial, from the following experimental data: alkaline hydrolysis of derivatives of the axial dihydroiso acid-I yields the more stable equatorial dihydro acid-I; the methyl ester of the equatorial acid is more rapidly hydrolyzed than that of the axial acid; and nitrous acid deamination of the primary amine resulting from Curtius degradation of the equatorial dihydro acid-I yields the corresponding alcohol of the same configuration, while the epimeric amine, obtained in the same way from the axial dihydroiso acid-I, suffers elimination (dehydration of the unstable alcohol) on deamination.



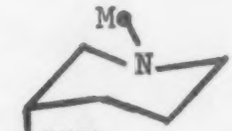
dihydro acid-I
(equatorial)

dihydroiso acid-I
(axial)

Hydrogenation of the double bond in position 9, 10 of ring D places the hydrogen at position 10 either cis or trans in relation to the hydrogen already at position 5. Since the

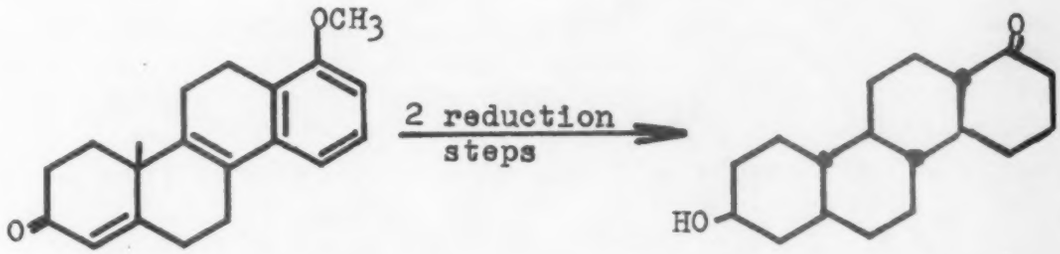
dihydro acid-I and dihydroiso acid-I are more stable they must have rings C and D trans-fused (analogous to trans decalin). The two remaining isomers, dihydro acid-II and dihydroiso acid-II, must have rings C and D cis-fused (analogous to cis decalin). Dihydroiso acid-II is the more stable of the two (its methyl ester is more rapidly hydrolyzed) and thus has an equatorial carboxyl group.

dihydroiso acid-II
(equatorial)



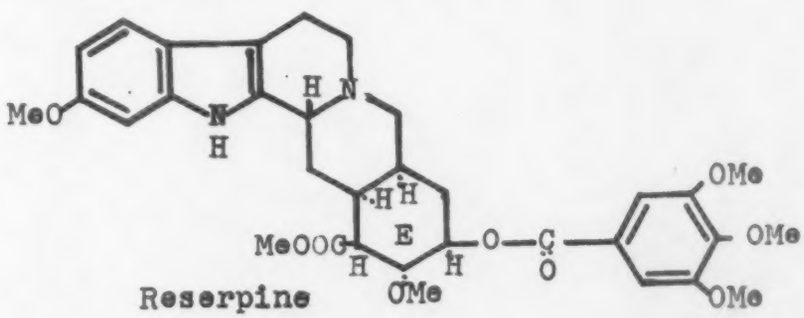
dihydro acid-II
(axial)

In the recent total synthesis of a steroid, epiandrosterone, one of the key intermediates involved the introduction of 6 asymmetric centers in a stereoselective reduction so that the spacial arrangements of atoms in this intermediate would be the same as in the final product



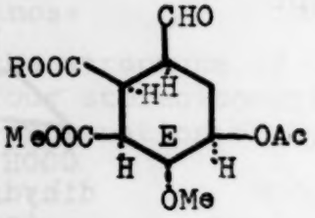
The reasoning behind the reactions and conditions that were chosen to accomplish this had its foundation in conformational analysis which enabled the chemists to predict the preferred spacial arrangements of atoms that would result from a given set of reaction conditions.

The recently reported total synthesis of reserpine also involved a series of stereoselective reactions to obtain key intermediates in which the stereochemistry was the same as in the final product



Reserpine

Of the six asymmetric carbon atoms in the molecule, five of them are adjacent to one another in Ring E. By a well chosen series of reaction conditions which, on the basis of the principles of conformational analysis, were predictable as to their results the problem presented by the stereochemistry of Ring E was solved by the synthesis of the labile intermediate



containing the five asymmetric carbons properly oriented. This was then condensed with 6-methoxy tryptamine, followed by subsequent reactions to complete the total synthesis of the alkaloid.

REFERENCES

1. Djerassi, D., Application of Optical Rotatory Dispersion Studies to Structural and Stereochemical Problems in Organic Chemistry, Organic Chemistry Symposium, American Chemical Society (1957).
2. Klyne, W., Progress in Stereochemistry, Academic Press, Inc. (1954).
3. Newman, M. S., Steric Effects in Organic Chemistry, John Wiley & Sons, Inc. (1956).
4. Barton, D. H. R. and Cookson, R. C., The Principles of Conformational Analysis, Quarterly Reviews of the Chemical Society of London 10, No. 1, P. 44 (1956).
5. Woodward, R. B., et al, The Total Synthesis of Reserpine, Tetrahedron 2, 1 (1958).

DISCUSSION

Youngken Jr.: What is the stage of development of the in vitro process of photosynthesis--is it economically feasible now?

Parks: Not yet.

Youngken: What of the synthesis of reserpine?

Parks: Same answer.

Youngken: Are particular steps of so great difficulty that they are impractical?

Parks: Many steps are involved--some of the intermediates are difficult to get and expensive. They are not available in sufficient quantity to make synthesis practical as yet.

Dunn: Has this method of approach been used with the sex hormones?

Parks: Yes, some work is being done on the difference in physiological activity in cortico steroids--how the molecule fits down into the receptor site of the tissue surface; what makes it more or less effective in reaction. Future work will be on the evaluation of molecular relationship to substrate form.

Sim: How easily and what procedures are used for extracting a fat or fatty product from its source and isolating the product? Some conditions would crack the fat.

Parks: If any procedural method effectively changes one configuration to another the procedure is arranged to overcome that difficulty.

Sim: I've noticed that sometimes the cruder forms are more active than they are after isolation. I thought the change was due to breakdown of the fat in its isolation.

Parks: If the derivative is changed you may get something different than the original material. We should be able to refine our separation methods to avoid this sort of thing.

THE LITERATURE OF PHARMACOGNOSY

James E. Dusenberry

INTRODUCTION

In accepting the invitation from the Teacher Seminar Program Committee, little did I realize at the time, that I was accepting a responsibility that borders on the infinite or even the impossible.

By bordering on the infinite I mean literally that. I now know what the space scientist means when he uses the term of weightlessness in the infinite limits of space. Once you delve into the literature of pharmacy you readily acquaint yourself with the immensity of it all. I hesitate to enlarge on my use of 'impossible' because as teachers we should limit its usage only to its interpretation in the writings of others.

My second response was to contact the pharmacognosists themselves; because pharmacognosy has developed into such a broad field of endeavor embracing so many and varied disciplines and involving numerous collateral sciences. I felt that because of this diversification of interest in our discipline that it would only be possible to prepare an informative presentation by a collective effort of those concerned.

To my knowledge, the only way of collecting the combined thinking of such a dispersed group would be to send a questionnaire. I am sure that you will agree that it is the most convenient, at least for the person undertaking the assignment.

For those who answered the questionnaire I want to apologize for imposing that added burden upon your already busy lives and I trust that you will understand the importance of participation in efforts such as this.

I realize that many of you have long been subjected to these questionnaires and I quote,"have become allergic to such nonsense, especially after repetition every few years," unquote.

However, beyond the fact that these collections of literature information have been compiled, printed, and distributed, on occasion in the past, nothing more has been done in the way of an orderly systematic method of preparing current bibliographies on items of pharmacognostical interest, let alone

abstracting some selected list of journals. I would like to enlarge on this a bit later.

From those questionnaires returned I have attempted to prepare a Guide which might be helpful to the young pharmacognosist, or otherwise, who might be seeking information on the literature available.

It is of course true that we are all familiar with what we might choose to call "basic references" and there would be little need to even mention their usefulness. While they of course are included in this Guide the main purpose is to provide some of the sources of information with which you may not be familiar, to call your attention to new texts and serials, etc., and to provide such a list in outline form for your convenience.

From the questionnaires I gather that to several people teaching pharmacognosy, reference material is comprised chiefly of that which has been referred to as "basic" or "essential". This fact alone limits his scope of knowledge which in turn limits the scope of his interests and probably the effectiveness of his teaching. Thus, it is hoped that the Guide will serve as a tool toward expanding both areas.

The compiled lists can be termed neither basic nor essential--but are intended to serve as tools in your selection of reference materials. It should be emphasized that I am not suggesting that you have everything in the list available - but merely that it is an opportunity to select and further to know what other pharmacognosy teachers use in their pursuits.

Many of you have access to excellent libraries where many of the listings can be found. In any case, they can be obtained on interlibrary loan from one of the member colleges. What you need in the pharmacognosy department of your school depends upon the scope of your activities and the type of teaching you hope to perform.

While the questionnaire for extracting ideas, opinions and other information from persons engaged in some segment of pharmacy has been somewhat over-worked, it has yielded certain useful information. Foremost, of course, has been the opportunity for comparison of certain aspects of your school with those of the member colleges and other information which may be of value in improving some area in your institution. I am certain that the library, including the literature collections

pertaining to pharmacognosy, has been improved by such efforts.

While most of these findings have previously been distributed to the schools, for the younger teacher, I might call attention to the listings of books and periodicals which have appeared in The American Journal of Pharmaceutical Education during the past twenty-one years. These are to be found in the bibliography. (1-8)

It would not be feasible to attempt any coverage of the historical literature of pharmacognosy other than to mention the monumental contributions of Tschirch and his survey titled "Handbuch der Pharmakognosie." (9) Reference to this and other bibliographic materials, in English, related to pharmacognosy are to be found in a most excellent recent paper by Hoch. (10) Likewise reference should be made to the many valuable contributions of the American Institute of the History of Pharmacy.(11)

I also have chosen not to speak on the subject matter of current pharmacognostical literature, this being the prerogative of several other seminarians, but rather to concern my remarks with the current status of the literature.

FOREIGN LANGUAGE

Commenting briefly on the question in the survey concerning foreign language publications, the results indicated that most individuals have considerable difficulty in translating the foreign literature. Some, no doubt, who expressed little difficulty possibly do not expose themselves to it. Of course, this is contradictory to our graduate school transcripts which solemnly assure us that we can read German, French, Spanish or perhaps Russian. Many, however, readily admit that they can't and don't, or, can and won't.

Although today much of our scientific progress is recorded in English, the numerous important contributions in other modern languages should not be overlooked. It is estimated that there are some 55,000 journals appearing, containing 1,200,000 articles of significance for some branch of research. In the fields covered more than 60,000 different books are published annually, and over 100,000 research reports that remain outside the normal channels of publication and indexing. (12) To get some idea of the number of foreign periodicals one merely has to thumb through the World List of Scientific Periodicals which indexes over 1,500 journal titles, a breakdown will show 58% of the titles are in foreign languages,

and the remainder in the English language. (13) It might be of interest to add that one-third of the titles emanate from the Western Hemisphere, and two-thirds from the rest of the world.

Likewise, results of the questionnaire indicate that a higher percentage of foreign language articles pertaining to pharmacognosy are appearing in the literature.

Many of these articles are not found in the major abstracting publications. No doubt this is due to their intermediate nature between the fields of chemistry and pure biology.

The only alternative we have is to better prepare ourselves and certainly our students. We must accept this necessity of learning to read, if not to speak, the language of eminent colleagues in other lands.

We have all been taught that science is international, or even universal, and that people in sciences must be able to communicate with each other. Now, less than ever before, can we afford to overlook our shortcomings in the languages.

This age-old necessity is now sharpened by international tensions and rivalries; the pursuit of knowledge has become a race against time.

CURRENT NEEDS

Perhaps no problem facing the individual scientist and teacher today is more defeating than the effort to cope with the flood of published scientific research, even if it is limited to one's own narrow specialty. Not only does the present situation present a seemingly unsurmountable task to the individual, limiting the progress of the profession, but also offers a grave threat to the integration of scientific knowledge.

In many of the areas of scientific endeavor some efficient indexing and abstracting systems have appeared. Such systems become daily more essential because of the tremendous increase in scientific publications during the past fifteen years. Because of this recent phenomenal growth of pharmaceutical literature and of that of allied fields it is imperative to bring to your attention the need for studying better methods for dealing with this vast literature.

The brief survey indicates that libraries of our schools of pharmacy are much improved over the past few years. Budget allotments have increased considerably which of course has resulted in vastly improved collections of books and periodicals. Much of this improvement is due to the efforts of the AACP officers, Library Committees, and of course the Journal of Pharmaceutical Education.

In spite of the fact that progress has been made in our libraries, with their enlarged literature collections we can not hope to keep abreast of the literature increase itself. While our collections have increased numerically the available literature has increased exponentially.

It becomes alarmingly apparent that something must be done. It no longer suffices to rely on books and periodicals to which your library subscribes to keep abreast of developments in a discipline, especially in our discipline. Even to keep progress in sight we must improve present methods and devise new ones for meeting this problem.

It is evident that we should and must improve the status of the reference services in our pharmacy libraries if we even hope to come in contact with this literature.

Provision for these necessary functions would involve at least the following three requisites. They are: (1) Presence of a reference librarian trained in the pharmaceutical literature; (2) The provision of improved bibliographic sources such as indexing and abstracting services; (3) A cooperative effort on the part of the pharmaceutical profession to see that reference services are provided.

CONCERNING THE REQUISITE FOR ADDITIONAL TRAINING FOR LIBRARIANS

It should be emphasized that our librarians have been in no small way responsible for the improvement in our pharmacy libraries. Currently more and more pharmacy libraries are being staffed by trained librarians. However, today our demands go beyond the need of people qualified by their basic training to be called professional librarians. The current situation in literature demands almost a specialist in pharmaceutical literature. It would not be wise, at this time, to advocate a distinction in basic training for professional librarianship between pharmacy and some other type library. However, it would be extremely beneficial to the library

service that the librarians would be able to perform if the member colleges would make provisions for their librarians to attend classes of the type conducted by Winfred Sewell, Librarian for Squibb Institute in Medical Research, at Columbia University this summer. A Reference Librarian from our school attended this seminar and, incidentally, was the only one attending from education. It was emphasized that more librarians should have background in pharmacy or related science fields. By attending courses like this, or seminars of the type conducted by the Pharmaceutical Section of the Special Libraries Association, they would become familiar with the intricacies of the pharmaceutical literature.

CONCERNING THE REQUISITE OF BIBLIOGRAPHIC SOURCES

Unlike the pre-clinical faculty in a school of medicine, most pharmacy faculty members are required to teach through the regular school term and frequently during the summer sessions. This means that each faculty member must wisely allocate the free time that he should spend in library and laboratory research. Obviously the busy teacher must increasingly depend on more efficient bibliographic aids, indexes, abstracting services and review journals in order to become familiar with current work, and to permit concentration on selective reading of original work.

More emphasis should be placed on original work. There is also an urgent need for more efficient bibliographic sources to help eliminate duplication in research efforts. With the all-too-common practice of write-for-the-sake-of-writing, or publish or perish, the literature is rapidly becoming a multiplicity of duplicity. This would be avoided if our investigations were more characterized by original, intellectual conception, were prefaced with more thorough literature study and were pursued with a well-meditated conception of experiment.

FINALLY CONCERNING A COOPERATIVE EFFORT ON THE PART OF THE PHARMACEUTICAL PROFESSION

With the passing of Pharmaceutical Abstracts in 1947 we lost a valuable, centralized source of literature information. As you know, it was discontinued due to the expense involved and the delay encountered in the preparation of the abstracts. However, during its existence, it was the most comprehensive abstract work in the English language on pharmaceutical papers. It no doubt was true that a high percentage of its articles were abstracted elsewhere, but as has been pointed out by

Cowles, (14) the remainder of its contents served as reliable clues to current literature.

Sewell, (15) points out that no single service lists most of the important pharmaceutical papers and that Chemical Abstracts, Chemisches Centralblatt, Biological Abstracts, and to a lesser extent, Excerpta Medica omit many important pharmaceutical papers appearing in journals they list as abstracting. Pharmaceutical Abstracts supported by a cooperative effort of the various segments that comprise the pharmaceutical profession would have done a great deal to lessen literature problems that we face today.

Cooperative information processing in the pharmaceutical industry is not new. The Special Libraries Association, through their Committee on Pharmaco-medical Non-serial Industrial Publications issues a so-called Copnip List quarterly. It contains titles and sources of pamphlet material of interest to industry.

Still another committee compiles Unlisted Drugs which appears monthly. This is a contribution of twenty some odd participating libraries which regularly check certain assigned journals for new drugs. It does not give complete abstracts, but consists of certain standardized information.

In addition, the Pharmaceutical Section of the Special Libraries Association in 1955 presented a proposal to the American Drug Manufacturers' Association to establish an abstracting service in the pharmaceutical field. Emphasizing that there is no single service or combination of services which supplies adequate abstracting and indexing from the pharmaceutical point of view, the plan calls for, according to Sewell, (16) a centralized agency with paid abstractors, which would produce semi-monthly abstracts from 200 selected journals, an index with each issue, to be cumulated every six months.

Strieby (17) reported on an invitational meeting held in 1956, attended by a "cross-section of research scientists, editors, company executives, librarians and government specialists." The purposes of said meeting were "to foster cooperation in bibliographic and abstracting sources; to determine the extent to which a community of needs in the pharmaceutical field can be brought together for effective cooperation and to consider opportunities for the avoidance of duplication among competing services."

This report did not elaborate on any concrete ideas that might have been reached by the group, however, it did conclude with, and I quote,"A need for further exploration of the purposes of a cooperative service as well as its type, scope and cost," unquote. Whether or not additional meetings have been held for the same worthy purposes, I do not know.

Now the purpose of my mentioning this was not merely to point out attempts at a cooperative literature service, or to report on seemingly negative results, but to point out to you that according to the representatives listed as attending this meeting, there was a glaring lack of anyone from pharmaceutical education.

We in education are charged with the responsibility of developing and maintaining a program for the education and professional preparation of pharmacists. It would be well for all of us to occasionally read through the stated objectives of the Pharmaceutical Survey. Can we attain these aims and objectives? can the goals which were stated so clearly and in such detail be achieved if we do not at least keep abreast of our respective disciplines? No, we can not. Keeping abreast is not enough. Remember, it is also possible to stand abreast, as in a military review, but little progress will be achieved. This is all right for a review and that is just about the point that we in pharmacognosy stand today - in review.

Those who rely solely on both editions of the APhA Journal, or other publications within the profession, can not hope to keep up with the literature. These are composed primarily of articles written by other educators, including their graduate students, or that smattering of papers that eventually trickle from the great laboratories of pharmaceutical industry. Some indicate that they obtain a lot of information by reading various of the house organs. Certainly they are replete with interesting information, but most are hardly of that quality that stimulates intellectual conception.

While we are charged with the responsibilities of the educator, could we not better perform these accepted responsibilities if we were better informed on current practices, methods, etc., from the industrial segments of pharmacy?

If we as teachers continue to rely on texts as sole sources of methods, procedures, etc., is there not danger of continued propagation of discontinued and out-dated information?

With all due respect to our more industrious, devoted, colleagues we must hold that texts, essential as they are, must be supplemented with current and ever-changing ideas.

This practice tends to leave the student with the impression that the text is the only authority. This is seldom true, even if it were possible to keep the text current.

Would it not be extremely beneficial to the researcher in schools of pharmacy to have reasonable access to the elaborate extensive literature files of industry? Think of the amount of time these excellent bibliographic guides would save the individual, even if the information were available and obtainable at, or through, his own institution. To prevent a duplication of effort, contributions in the way of an additional IBM card (or similar mechanical processing device) could be sent to the Central APhA offices where they could be processed and distributed on request. True, problems would have to be ironed out, but as Barbara Cowles, (18) stated in 1950 in an article concerned with the Indexing of Pharmaceutical Literature, quote, "These are not insuperable problems. The key to them all is one word - cooperation." Unquote. Should the responsibility of providing adequate reference materials, their production, scope, format, and financial support remain a problem of the educator alone or should it rest on the shoulders of the entire profession?

Possibly those of us in pharmacognosy who are really interested in keeping up with certain original articles could do so more thoroughly and expeditiously if we followed a method similar to the one in operation by the Hospital Pharmacists. While they have both a bibliographic and abstracting service the duties are performed by a limited number of people. Understandably the literature pertinent to pharmacognosy is diversified. However, with a cooperative effort on a selected list of journals a lot could be accomplished by a few.

With such an effort at this time, we in American Pharmacognosy would be in a better position to make a contribution to the proposed International Pharmaceutical Abstracts, (19).

While we all take pride in the growing volume of information in our discipline, we may have a different feeling about keeping up with it or retrieving data on a specific subject. The Library should be a tool for creativity in the same manner as the laboratory. Needed information may be obtained frequently from the literature more readily and at a lower cost than work at a laboratory bench. The researcher in industry

has two competitive ways to solve a problem - in the laboratory or in the library, whereas, we in education have no choice. Either we pursue the literaure and progress or ignore the literature and retrogress.

As people in many other areas of specialization, Pharmacognosists too frequently are guilty of thinking that their specialty is an area unto itself, it is unique, different, separate, or in-between. As we well know, there are no borders or fences around it. Like so many other areas of science today, pharmacognosy is closely allied with, and touches virtually every other specialization. Actually, the most 'in-between' or 'intermediate' aspect of pharmacognosy is the current literature.

REFERENCES

1. Report for 1942 of the Committee on Libraries, Am. J. Phar. Educ., 7, 187 (1943)
2. History, Ethics and Literature of Pharmacy, ibid, 8, 491 (1944)
3. Report of the Committee on Libraries - Concluded, ibid, 9, 395 (1945)
4. Report of the Committee on Libraries, ibid, 13, 669 (1949)
5. Report of the Committee on Libraries, ibid, 14, 613 (1950)
6. Report of the Committee on Libraries, ibid, 16, 633 (1952)
7. Books, Reference Works and Periodicals Literature Recommended for College of Pharmacy Libraries, ibid, 19, 481 (1955)
8. Report of the Committee on Graduate Programs, ibid, 21, 247 (1957)
9. Tschirch, A., "Handbuch der Pharmakognosie", C. H. Tachnitz, Leipzig, 1905-25, 3 Vols.
10. Hoch, J. H., Am. J. Phar Educ., Spring, p 155 (1959)
11. Sonnedeker, G., ibid, Spring p 143 (1959)
12. "Availability of Scientific Information", Nature, 183, 136 (1959)
13. Rodgers, F., Bull of Med Lib Assn, 39, 34 (1951)
14. Cowles, B., Bull of Med Lib Assn, 39, 34 (1951)
15. Sewell, W., McCann, A., & Kelley, I., Advances in Chemistry Series, American Chemical Society, Washington, D. C., 1956, p. 209
16. Sewell, W., Spec. Lib., 48, 189 (1957)
17. Strieby, I. M., "Documentation in Action", Rheingold, New York 1956, p. 344
18. Cowles, B., Bull of Med Lib Assn, 39, 34 (1951)
19. Francke, D. E., Amer J of Hosp Phar, 15, 961 (1958)

DISCUSSION

Pokorny: Will you please comment on your ideas of getting undergraduate students into the reference literature.

Dusenberry: Give them assignments.

Lord: How many are interested in the new publication listing the Tables of Contents. Does anyone here subscribe to it, and is it of any help?

Van Horne: We subscribe to it and find it of some value.

Call: We have examined it thoroughly--have found it not as helpful as Current List of Medical Literature which is cross indexed for article content, topics that may occur in the text as well as titles. We have decided not to use the Table of Contents publication.

Beal: In my experience this past year at Wisconsin I found it helpful in keeping up with current work. It is simpler to scan it than to go into the library and go over all of the separate journals. This makes it much easier to watch for articles that will be coming out--very time saving.

Cole: We have a system at our college that originated at the University of Utah--the current literature is placed on a table for a week and removed at the close. By going into the library on the same day of each week, one can quickly glance over the current literature of his interest.

Ramstad: At the University of Oslo we circulated all journals that pertained to the work of the local department of the institution via the offices of the administration. At Purdue we have some services furnished by the department of chemistry. They list all of the articles from the journals they receive. These are mimeographed and distributed to those interested. The same service is available from agriculture. However, we in pharmacy have no such list for our literature.

Zopf: We have a similar service between pharmacy and botany. We have a limited number of journals that are circulated. We have had to place a time limit on these as they are lost in certain offices which keeps them away from the

library too long and thus they are not available to the students.

Claus: We found at our school that many times the students have gotten the information before the faculty--therefore the list of articles is given to the staff. The journals are then circulated through the faculty for 3-4 days then placed in the library. None have been lost as yet.

PHARMACOGNOSY AND THE COMMUNITY

N. M. Ferguson

The pharmacognocist has long been a central figure in community life. Primitive man learned how to use crude drugs through trial and error, experimenting first on himself and then, when results were obtained, he used the same drugs on his family and friends. Eventually he became somewhat of a specialist in his small community in the collection, identification, and use of crude drugs. Usually he combined a smattering of magic and religion with the treatment, thereby hoping to make it more effective. According to Tschirch, such crude drug specialists, the pharmacognocists, became the forerunners of pharmacists and physicians of today.

Down through the ages the knowledge of drugs was transmitted from father to son the secrets often remaining in one family for generations. The Egyptian priests responsible for drug collection, identification, and administration followed this custom and thereby added greatly, during each generation, to the total knowledge of drugs.

In early Greek times a group of pharmacognocists known as the rhizotomists were responsible for the collection and use of plant drugs in the community. They were quite influential in drug practice from the time of Homer to that of Hippocrates and provided in their writings accurate descriptions of crude drugs for identification purposes as well as methods of preparation and administration. These writings served as the chief source of information concerning drug usage for the Hippocratean school and indirectly formed a basis for later writing on pharmacy and medicine. Many of the drugs described by the rhizotomists are still in use today.

Through these many hundreds of years, since the beginning of communal life, the collector of plant drugs has occupied an important position in the community. Even today among the primitive tribes of South America and Africa the medicine man or witch doctor, as he is sometimes called, is in reality a pharmacognocist. He is responsible for the collection, identification, preparation and administration of drugs. But in addition to these he is religious advisor and very often criminal judge as well.

During Socrates' time, pharmacognocists were in a sense state executioners in that they were required to provide a

proper poison for prisoners, traitors, political enemies and in some cases elderly people who became a drain on the economy of the city or state. Plato, in his Dialogues, describes the death of Socrates and mentions the "Cup of Hemlock" commonly used during that time as a state poison. This was a rather elegant method of eliminating undesirable people. Very often the accused would gather his friends around him, wine and dine them and, at the height of the festivities, "quaf the Cup of Hemlock." The Greeks not only lived well but they also died well. Many references are made in Greek literature to this practice.

The use of Tanghin, Tanghinia Venenifera; sassy-bark, the bark of Erythrophloem guineense; and Esere bean, the seed of Physostigma venenosum, further attest to the use of crude drugs and their preparations in tribal, communal and state ceremonies in determining guilt by poison. Among the tribespeople of Africa and Madagasgar, Tanghin is probably still in use. This custom was widely practiced even as late as 1850 and was responsible for the death of more than six thousand natives in a single year. Old and young alike would gather for the ordeal and drink the Tanghin hoping thereby to prove that they were not bewitched. The "tribal pharmacognicist" or witch doctor, however, received a fee for administering the poison and, as a result, was happy to be paid for ridding his tribe of bewitched members. Like sassy-bark, and Esere bean, Tanghin was also used in cases involving political crimes, civil cases, and even in cases of petty theft.

In reading the history of certain pagan religions it is found that the use of crude drugs plays an important part. Indeed the use of coca leaves in connection with religious rites in some of the West Indies Islands and certain parts of South America is still practiced. At the present time Mescal-buttons are being used in the religious rites of certain Southwestern American Indian tribes as has no doubt been their custom for hundreds of years.

Nor should the influence of pharmacognosy on the community with respect to their drug industry be overlooked. The cultivation of drugs is a community project in many parts of the world providing employment for the people and income for the community. The collection of drugs from plants growing wild requires that the individual pool his collection with his neighbors so that the mechanics of sorting, packing, selling, shipping to market may be performed efficiently. The cultivation of cotton, tobacco, cinchona, cloves, and even opium

often requires the combined efforts of a whole community. When a crop of Turkish poppy capsules is ready for incising, the whole community lends a hand since the work must be done during a very short period of time as must also the collection of the crude opium.

It is rather interesting to note that although some drug plants are produced almost entirely through cultivation, a considerable tonnage of crude drugs used today **is** still gathered from plants growing wild.

Commerce in crude drugs and spices has been an important source of income for communities since man first left his home to see what was beyond the hills or plains which surrounded him. Early trading stimulated an exchange of ideas between widely separated countries and improved the cultures of all peoples concerned. Indeed, the discovery of America was the result of an attempt to find a shorter route for shipping drugs, spices and other commodities between European ports and the East.

The cultivation and collection of crude drugs passed into the hands of the monasteries during the dark ages. Here certainly was a community project since the crude drug and its preparations were handed out to the citizenry or the community. This project kept the knowledge of crude drugs alive during the long periods when educational training for even the select few was not available. As the universities began to develop throughout Europe there was a revived interest in drug cultivation, identification, and preparation for use in medicine. Since the universities became the centers of pharmaceutical and medical training they engaged in the propagation of drug plants. After a time community owned drug gardens were maintained to assure an ample supply of the commonly used drugs. In many cases a pharmacist would cultivate the plants he needed in his practice and occasionally societies of apothecaries operated a large drug garden producing crude drugs for the use of their members. Indeed the earliest reference to pharmacy in the state of Georgia has to do with a grant of 5,000 pounds, in 1732, from the London Society of Apothecaries to the colony of Georgia, which colony was established for the purpose of cultivating crude drugs for shipment to England and ultimate use by the members of the society.

Nor were all of the community related aspects of pharmacognosy commercial in nature. Many cultural aspects of pharmacognosy besides beautiful drug gardens are known to us.

There are many references to the use of crude drugs in the Bible which attest to their use at that time. Many poems and plays as well as works of fiction refer to drug plants, their beauty and use. Indeed stamps and coins of many countries stress the importance of drug plants.

Since the medical practice was closely accompanied by witch-craft and religion, frequent references to crude drugs are found in the literature of many peoples. Shakespeare makes many references to drug plants in his works as do other outstanding writers.

Other cultural aspects of pharmacognosy deal with the advice to herb gardeners and flower lovers concerning the cultivation of drug plants. Many pharmacists through their knowledge of pharmacognosy have served as speakers before garden clubs, service clubs and similar organizations, and in so doing have added to the culture of the community. Included in such an address should be warnings concerning the dangers from common poisonous plants such as castor bean plants, Buckeye trees, poison ivy, poison oak, to mention a few, since children quite often become poisoned through contact with such plants.

From a practical, everyday aspect the pharmacognocist serves his country, his state and his community by controlling the importation of drugs. His job is to see that only drugs which are of the correct genus and species and of high activity are allowed to enter the country for use in medicine. Similarly drugs collected in this country either from wild or cultivated sources must be approved by the pharmacognocist before they can be used.

The pharmacist serves as an expert pharmacognocist when he identifies plants grown in the garden or in the field and provides information concerning their constituents to the physician or poison control center. Often pharmacists in farm communities make use of their pharmacognosy training in identifying range plants poisonous to livestock and poultry. Some pharmacists have prepared herbarium mounts of the common poisonous range plants found in their community. This has been a great help to the farmer and rancher in his attempt to eradicate these plant pests.

Herb garden fanciers have also been properly guided to a better, more productive garden through the help of the corner pharmacognocist. Many pharmacists have been called on by the local, state and federal authorities to identify marihuana, opium, and other various narcotic drugs and their principles

when they were used indiscriminately to produce addiction. In this connection also, several pharmacists, through their knowledge of narcotic drugs, have served on narcotic control councils.

The pharmacognocist, through his knowledge of rodenticides and insecticides, is also helpful when he serves on drives to rid the community of rats, and insects, thereby contributing to the health of the citizens. He also serves as a source of information for allergy sufferers, when their affliction is caused by plants. He should be well versed in pollen counts and time of pollenation of common offenders.

Many pharmacognocists serve as advisor on Public Health measures involving communicable diseases. Through their training in bacterial products they are acquainted with the up to date information on these products together with their effectiveness, dose, availability and cost.

The pharmacist-pharmacognocist should be active in all community drives for the control of all diseases and should identify himself as a pharmacist and pharmacognocist with any drive that has as its ultimate goal a cleaner, healthier and better community in which to live.

DISCUSSION

Question: You made reference to your poison center--will you tell us about it?

Ferguson: The Poison center was set up--manned 24 hours daily at the Polio Center--our faculty listed their specialties and contributed information to the poison center on filing cards--information that could be used immediately upon a call. This included trade names, constituents, common names. The pharmacologist wrote up characteristic reactions to the poisons, proper antidotes. All departments of our college took part. We have a good list of proprietaries, insecticides etc. and we think we have a complete list and are able to do a good job of public service.

Zopf: Our hospital pharmacists have made up their own cabinet and keep records on hand. It is surprising to see the interest of the physicians in the use of this. Items are

included from the headquarters in Washington. It is not necessary to compile all of the information yourself. Ours includes common antidote, charts that are in our hospital formulary, etc. It is not unusual for me or our hospital pharmacist to be called nearly every night about shoepolish, fuels, houseplants etc.

AN EDUCATIONAL PSYCHOLOGIST LOOKS AT TEACHING IN PHARMACOGNOSY

N. L. Gage

In their volume on The Pharmaceutical Curriculum, published for the American Association of Colleges of Pharmacy in 1952, Blauch and Webster wrote as follows about pharmacognosy:

> Much emphasis has been placed on rote memorization rather than on constructive thinking concerning problems. This has tended to devitalize the subject and to make it uninteresting to students. The analytic viewpoint so widely prevalent has not fostered a creative attitude.
>
> What is now needed is a new point of view which recognizes the more extended and practical service that pharmacognosy can render. In accordance with this point of view, a body of content has to be organized and taught which presents a coherent and practical account of currently important biological substances. These materials should be presented to students in accordance with what is known about the psychology of learning and by the use of modern teaching techniques (Blauch & Webster, 1952).

Since I was invited to speak to you by one of the authors of the report from which I have just quoted it is obvious to me that I should speak to you about what the psychology of learning and modern teaching techniques might have to offer to the teaching of pharmacognosy.

Whether what I shall have to offer will be sensible or practicable remains to be seen. But let me at least try. How does an educational psychologist think about the problem of presenting subject matter so that it will be learned with maximum value? My own thoughts fall under five headings: (1) the problem-solving process, (2) the taxonomy of objectives, (3) the proper use of lecture and discussion methods, (4) the proper design of examinations, and (5) the motivation of the college teacher.

The Problem-Solving Process

First, the problem-solving process. For some time now, many teachers have realized that mere presentation of subject-matter to students was far from adequate to insure that the students would learn the material in such a way that it would be remembered and transferred to out-of-school situations. Teachers have realized that the more coherent and well-organized the subject-matter was, along lines inherent in the subject, the easier it would be to learn. But the organization has to be meaningful to the learner, not merely to the teacher. And sometimes what is a logical and orderly sequence of ideas to the teacher is not that for the student. How can we proceed so that what is to be learned takes on sequence and continuity for the student, and not merely for the instructor? One way is by arranging for students to go through the problem-solving process in the course of their learning such material as pharmacognosy has to offer (Morse & Wingo, 1956; Cooper, 1958). This means that students must first confront some problems, preferably those that they can identify themselves with help from their instructor. The problem should be something genuine to the student, some obstacle between him and some goal he would like to reach. In pharmacognosy, I can only guess as to what such problems might be. The first part of the course might provide a survey of the field in which problems might be located. A student's problem might then be to compare the different ways in which the subject-matter of pharmacognosy can be organized. Or the student might want to make a detailed study of a certain class of drugs. Or he might want to dig into the pharmacognosy problems involved in the legal regulation of narcotics. My examples may be poor ones, but the nature of the problem should be clear: it should be genuine to the student, relevant to the course, feasible for the student to work on, and productive of a variety of experiences as the student goes through the remaining steps in the problem-solving process. These remaining steps are well-known in the abstract, even though they are seldom followed in any such sequence: the problem solver evolves hypotheses and derives their testable consequences and then carries out tests or experiments or other studies to see if the hypotheses are supported or refuted.

At any rate, there is no question in my mind but that educational psychology says that teachers should give their students--even beginning students, immature and ignorant students--greater opportunity to engage more in independent study, to get away from conventional textbook and classroom instruc-

tion, and to work with primary sources in the library and the laboratory. The problem-solving orientation is designed to make students less dependent on their professors, to use reference sources of their own choosing, to take greater responsibility for their own learning.

There is a danger in such teaching that students will not get a well-rounded survey of the field of subject-matter, of the whole discipline of pharmacognosy. Hence it is desirable that some general reading assignments be made. But beyond a minimum of this sort of thing, the studies of problem-oriented teaching and learning show that students do just as well on general achievement tests over the whole subject as do students who have spent a whole semester doing assignments given them by the instructor, or going through a textbook chapter by chapter. And the problem-process students, it is usually concluded, have learned more about how to think in the subject-matter of the course, about how to get along on their own and apply what they have learned in real-life situations. What they have learned seems more vital to them, better organized in their own minds--even if it departs from the elegant organization that some textbook author was able to impose on the subject-matter in order to achieve solutions of his own intellectual problems.

The Taxonomy of Educational Objectives

Now let me turn to a second possible contribution that educational psychology might make. I have examined the statements of objectives in the volume on the pharmaceutical curriculum. These statements are composed of two kinds of terms, those referring to the content of pharmacognosy and those referring to behaviors that students should be able to carry out with those contents. Examples of content are such phrases as "the constituents of products of biological origin having current medicinal and pharmaceutical importance and of their preparations." Another example of content is "the pharmaceutic and therapeutic applications of natural products in pharmaceutical preparations and medicaments." Or finally "the methods by which products of natural origin are evaluated." And what is a student supposed to be able to do with these **kinds** of content of subject matter? The answer lies in the two terms that occur repeatedly in this statement of objectives, namely, "knowledge" and "understanding."

Now it so happens that in recent years a group of educational psychologists have devoted themselves to the definition

and analysis of these two terms. I am referring here to the Taxonomy of Educational Objectives published in 1956 by a group of university examiners (Bloom, 1956). In this Taxonomy the terms knowledge and understanding are carefully defined, analyzed, and illustrated. Sample test items aimed at determining whether these behaviors have been achieved are offered.

Knowledge is the more simple of the two kinds of cognitive behavior and it is defined as those behaviors which emphasize remembering, either by recognition or by recall, of ideas, materials, or phenomena. Although some alterations may be expected in the material to be remembered, this is a relatively minor part of the knowledge behavior. The process of relating is also involved to the extent that the student is expected to answer questions and problems which are posed in a different form in the test situation than in the original learning situation.

Understanding, a more complex kind of behavior, consists of various intellectual abilities and skills that emphasize the mental processes of organizing and reorganizing material to achieve a particular purpose. In the Taxonomy, these intellectual abilities and skills are behaviors called comprehension , application, analysis, synthesis, and evaluation. Comprehension in turn has three subcategories: translation, interpretation, and extrapolation.

Let me illustrate here only what is meant by the term application. Application is the use of abstractions in particular and concrete situations. The abstractions may be in the form of general ideas, rules of prodecure, generalized methods, technical principles, ideas or theories. Application requires not only comprehension--or ability to demonstrate knowledge and use of an abstraction when specifically asked to do so--but use of the abstraction without having to be prompted as to which abstraction is relevant or without having to be shown how to use it in that situation.

What the Taxonomy, or at least the kind of effort which it exemplifies, has to offer to the teaching of pharmacognosy should be readily apparent. Here is a way to spell out more carefully and in greater detail the kinds of behaviors that you may want your students to acquire in relation to the content of pharmacognosy. Here is a way to communicate more clearly to yourself and to your colleagues what it is that you as a teacher want your students to achieve. The very effort to clarify, in such ways as the Taxonomy illustrates,

what you mean by knowledge and understanding will almost certainly force you to think through more concretely the goals of your teaching. And once the goals have been more carefully formulated, your attention to methods of teaching and examining will also be more detailed and more realistic.

Lecture and Discussion

But even after objectives of instruction have been carefully worked out, they remain mere words until they get put into action through the behaviors of the teacher toward his students. Let us look briefly at some lecturing and discussing--two kinds of teacher behavior. As to lecturing, my reaction as an educational psychologist is the same as Samuel Johnson's of about 200 years ago. According to Boswell, Johnson said: "Talking of education, people nowadays have got a strange opinion that everything should be taught by lectures. Now, I cannot see that lectures can do so much good as reading the books from which lectures are taken. I know nothing that can best be taught by lectures except where experiments are to be shown." "Lectures were once useful; but now when all can read and books are so numerous, lectures are unnecessary. If your attention fails, and you miss a part of the lecture, it is lost. You cannot go back as you can upon a book." As one listens to the lectures that go on in many college halls, we are led to ask whether what is being communicated could not have been gotten across more efficiently by means of the printed or mimeographed or dittoed page. What is the advantage of lecturing over printing and reading? In too many situations, there is none except that it is a cheap way to keep many students busy and under the delusion that they are being taught. Where staff is unavailable, or too costly we can readily find the lecture method making a happy marriage of convenience with the college budget. But this does not mean that the offspring of this marriage is usually good teaching. On many occasions the lecture method is educationally and psychologically indefensible, however convenient it may be financially. After Paul Klapper had listened to many college lectures, he concluded that, in many instances, the content of the lecture could have been more effectively communicated by means of a few mimeographed pages than by means of the hour it consumed on the part of a single professor and several hundred students (Klapper, 1949). Most students can read even technical material far more rapidly than it can be spoken and heard. In too many instances, the lecture is, in my opinion, a kind of deception of themselves

and of their students which college faculties and administration find it convenient to practice. We must not let its convenience conceal the fact that it is a misuse of the time that students and teachers spend together.

All this is not to say that good lecturing is not great fun for both the lecturer and the listener. Jacques Barzun has written a persuasive defense of the lecture as a mode of teaching (Barzun, 1954). He says "Lecturing comes so natural to mankind that it is hard to stop it by edict. It simply turns into bootleg form." And, he continues, "Now what makes a lecture legitimate and good? The answer is--a combination of eloquence and personality...The lecture room is the place where drama may properly become theater. This usually means a fluent speaker, no notes, and no shyness about 'effects'. In some teachers a large class filling a sloped up amphitheater brings out a wonderful power of emphasis, timing, and organization. This meaning--as against fact--is the one thing to be indelibly stamped on the mind, and it is this that the printed book cannot give. That is why their hearers never forgot Huxley lecturing, nor Michelet, nor William James." But Barzun himself finally admits that "at the same time, it is also true that lectures alone will not suffice to teach, for the lecture method assumes that every member of the class comes in the same state of preparation and leaves with the same increment of knowledge. The fact is otherwise. Only individual attention to each student can keep the whole class abreast and truly teach. A lecture is a sizing of the canvas in broad strokes. The fine brush and pallet knife must be used close up to finish the work of art. This is why a normal three-hour-a-week class is usually broken up into small groups for the 'third hour' after the two lectures" (pp. 38-39, Barzun).

I grant that it is fun to listen to a great man lecture, just as it is an artistic experience to hear a Beethoven symphony played by the Philharmonic. And even if it is not an awe-inspiring figure that we hear, it is fun to listen to an ordinary man who lectures well. But I insist that for the objectives in most of the courses taken by college students, the lecture method--as employed by the mere mortals who become college professors--is unsuitable. There are times and places in life where it is necessary or convenient to do what is unsuitable. That is why lecturing will probably continue to be perpetrated in many college courses. For some budgets, with certain staffs and students, with certain facilities, there is no other way in which it is so convenient to

have teachers and students spend their time together. When it takes more money, more creativity, more imagination, or just more plain trouble than the teacher and the college can afford, then the lecture method provides the easy and cheap solution.

Some efforts have been made to spell out good uses of the lecture method. One writer (Buxton, 1956) says, "Although it is easier to say than do, it seems likely that the lectures in a so-called lecture course should try to teach the same ideas as do the reading materials and other components of the course, but to do so in ways which do not repeat, but rather reinforce, supplement, and illuminate."

If they are used, lectures should not be completely one-way declarative communications. Rather they should also be interrogatory. Even in the largest group, questions should be asked and pauses should be allowed in which listeners should try to answer the questions. Such give and take is generally considered to improve the learning from a lecture. It can be purely covert, and the listener can answer only to himself. Or the students may actually be called upon to answer out loud.

Students may also be permitted to ask questions and make comments of their own, to take a more active role. But this procedure becomes unwieldy when there are more than about 30 students in the group. When such student participation is allowed, we no longer have the lecture method. Now teaching is by discussion, and toward this method educational psychologists take a more favorable view. Genuine discussion cannot be replaced by reading, as is true of the lecture. But what is genuine discussion? It is <u>not</u> a free-for-all, in which anything goes. It is rather a more or less disciplined and restricted inquiry by a group into a problem. The students participate in a group effort to propound their solution, to elaborate their solution, to defend it against attack by the instructor and other students, to relate it to other ideas, to modify it as necessary in the light of the attack, etc. (Axelrod, 1949).

In conducting such a discussion, the instructor must insure that all students participate, that all students hear and understand what is being said, that he does not do all the evaluating of what is said, that the discussion has some structure and continuity, that lectures to insure coverage of material will not be misconstrued as part of the discussion, that

he does less rather than more of the talking than he does in non-discussion teaching, and that the discussion requires students to stretch their minds, to meet intellectual challenges, and to practice their skills of analysis and synthesis.

Valid Testing

The next consideration I want to mention is that of valid testing. The term validity in educational and psychological testing has a special meaning: validity is the degree to which a test measures what it is intended to measure. Tests given by teachers of pharmacognosy should measure the degree to which students have achieved the objectives of the course or of a part of the course. If certain objectives of the course refer to a certain kind of understanding, then the test should reveal whether the student possesses that understanding. And the trouble with too many tests is that they do not require the student to show the kinds of achievement, or behavior, that the teachers have set up as objectives of their instruction. Too many tests require merely knowledge--or ability to recall or recognize facts, definitions, methods, or abstractions--while the teachers who made up the tests refer to such objectives as understanding, comprehension, ability to interpret data, ability to apply principles, and so on. Educational psychologists draw attention to this lack of validity in achievement tests and try to show how validity can be improved. For the invalidity of the test, as we all know, drastically affects what students learn to learn. If they learn to expect examinations that emphasize rote knowledge of facts, that is what they will learn, no matter how glowingly the teacher's statement of his objectives refers to more lofty objectives.

How to make examinations more valid, so that they elicit the behaviors set up as objectives, is a question that we can only skirt here. Much has been written on this problem (American Council on Education, 1959). My purpose is merely to draw attention to the availability of this literature, and to suggest that most college teachers can get some good out of it.

The Motivation of the College Teacher

The last factor I want to consider--and perhaps the most neglected determiner of effective teaching--is the college teacher's motivation. Most teachers could already do a better job than they are doing. They have much in common with the farmer who told the county agent, "I already know much more

about farming than I want to know." And of course, the principal reason for inadequate motivation to teach on the part of college faculties is that good teaching is not rewarded as well as research and other activities are rewarded. Many college teachers are in conflict between doing good teaching and doing what leads to professional advancement. The good teacher who never publishes is likely to retire at the rank of associate professor. Most college teachers would like to do a better job, but it takes more effort, more time, some looking into the literature on teaching, and so on. In the meantime, there is the pressure to publish, especially early in the academic career when the instructor or assistant professor is struggling for tenure. Under these circumstances, a man's teaching often tends to be just good enough to keep himself from attracting unfavorable attention from students or deans. Where good teaching does not pay off, but where research, writing, and administration are highly visible and better rewarded, it is easy to see where the college teacher's heart is likely to be.

The problem is made worse by the fact that almost all of the college teacher's background, training, and tradition are on the side of improving his research, while virtually nothing has been done to help him as a teacher. When he gets his degree and embarks on his academic career, he suddenly confronts the fact that much of his working day is taken up with teaching. Since teaching is relatively unrewarded, and since he has not been given the tools and skills for solving his teaching problems nearly as well as his research problems, we should not be amazed that the teacher often finds his satisfactions not in his teaching but in his research. Teaching may become a frustrating and bewildering obstacle in his path to academic success.

What to do about the teacher's motivation is hence a major problem. How can we increase the rewards for good teaching and give teachers better training and traditions for the teaching phases of the academic life? In large part, improved motivation can be derived from changes in attitudes on the part of college administrators. When it becomes known that they place great value on good teaching, are alert to its manifestations in a member of the staff, are ready to reward good teaching as generously as good records of research publication, promote the excellent teacher without noteworthy achievement in research, as well as the distinguished research man who does not teach especially well, then an improvement in the staff's motivation to teach seems likely to come about.

But the administrator also has his problems. First, how can he find out who the good teachers are, and how can he run counter to the traditions of the academic world, of his university, and of his discipline? Both the greater visibility of research contributions and the traditional emphasis on research, at least in major universities, make it hard for the administrator to give proper emphasis and reward to good teaching. The fact that there is no good way of evaluating college teaching as a basis for administrative decisions concerning rank and pay makes it extraordinarily difficult for the dean who wants to improve the incentives for good teaching (Gage, 1958).

Improved motivation to teach can also come from the development of a group atmosphere of steady concern with the improvement of teaching. The members of a teaching staff can get together frequently in small groups to consider their teaching problems. In a kind of continuing seminar, staff members can discuss teaching problems, propose solutions, analyze successes and failures in teaching, create a spirit of freedom to reveal one's shortcomings as a teacher and discuss them with one's colleagues. At the very least, such a continuing seminar can improve motivation to teach well, to use more of one's intellectual resources for the job.

Changing A Teacher

Finally, a word about the difficulties of changing a man's ways as a teacher. The methods and style of a teacher are highly personal matters, in the sense that they are deeply ingrained in his total personality, including his temperament, his values in life, his conceptions of what is fitting and proper. Changing anything as basic to a person as how he teaches cannot therefore be done by a mere lecture, by offhand advice and suggestions. Educational psychologists have found that teachers need to discuss, and observe, and talk things out, and sometimes work through emotional problems, before they can fundamentally change how they teach. It is facts like these that have led to the development of so-called "in-service" programs in which teachers can talk, work on committees, and engage in self-evaluation. Often the best place to start is with testing. To improve testing, teachers usually have to criticize and review their objectives and teaching practices. And almost before they know it, teachers are asking themselves searching questions about why they teach as they do and whether changes for the better cannot be made.

Conclusion

In accepting Dean Webster's invitation to speak to this seminar, I was attracted by the challenge of trying to say something worth saying about teaching in a field of whose content I am totally ignorant. Whether it is possible for an educational psychologist, or this one at least, to say anything of value to teachers of pharmacognosy, when he knows no pharmacognosy, is something that you have learned during the last half hour or so. But let me say in conclusion that what I have attempted runs counter to the spirit of the field I represent. Application of the concepts and principles of educational psychology to the teaching of any subject requires genuine interaction between the two fields. That is, only after active, prolonged give and take between us should we expect real payoff. The educational psychologist should have a chance to watch pharmacognosy teachers and their students as they grapple with their subject. And pharmacognosy teachers ought to have a chance to force the educational psychologist to get down to cases. The educational psychologist might then identify problems and phenomena of which the pharmacognosist had not even been aware. And the pharmacognosist could help in fitting psychological approaches and methods to his particular needs.

References

American Council on Education. College Testing: A Guide to Practices and Programs. Washington: American Council on Education, 1959.

Axelrod, J. and others, Teaching by Discussion in the College Program. Chicago: University of Chicago, 1949.

Barzun, J. Teacher in America. Garden City, New York: Doubleday and Company, 1954.

Blauch, L. E., and Webster, G. L. The Pharmaceutical Curriculum. Washington, D. C.: American Council on Education, 1952.

Bloom, B., and others. Taxonomy of Educational Objectives, the Classification of Educational Goals; Handbook I: Cognitive Domain. New York: Longsman, Green, 1956.

Buxton, C. College Teaching: A Psychologist's View. New York: Harcourt, Brace, 1956.

Cooper, R. M. (ed). Two Ends of the Log: Learning and Teaching in Today's College. Minneapolis: University of Minnesota Press, 1958.

Gage, N. L. "Ends and Means in Appraising College Teaching," in W. J. McKeachie, (ed.), The Appraisal of Teaching in Large Universities. Ann Arbor: University of Michigan, 1959,pp.58-64

Klapper, P. The Professional Preparation of the College Teacher, Journal of General Education, 1943, 3, 228-244.
Morse, W. C., and Wingo, G. M. Psychology and Teaching. New York: Scott, Foresman, 1955.

DISCUSSION

O'Connell: You spoke of the number of people who favor or avoid the lecture method. I'd like to hear about this specifically.

Gage: I'm very skeptical about lecturing. 90% of the time is much better spent between faculty and students in discussion than in lecturing. Students study much better by reading and then discussion--this will do better teaching than a lecture will. Research results on this point, however, are not very good. Irrelevant answers have been gotten because proper controls have not been set up.

Parks: How can one who has been accustomed to the lecture method get himself into a condition where he will use the discussion method effectively?

Gage: Mention may be made of "Buston--College Teaching--A Psychologist's Views" and a chapter from "Two Ends of a Log." However it takes more than just reading--one must try and retry--avoid and correct mistakes, etc. "Teaching by Discussion in the College and University" by Axelrod and Bloom is more detailed than the others on this subject.

Pokorny: Can you give your thoughts concerning college credits and hours? One can have a lot of discussion in a laboratory session.

Gage: I'd better not comment on these at this point.

Dunn: How long should a lecture last? How long is a student's period of absorption and retention? Is the seminar a practical way of dealing with a subject?

Gage: Seminars and discussion groups are about as effective a method of getting things done as any. On length of a lecture I can guess that the goodness of the lecturer is

such a variable--a good lecturer could keep a class enthralled for 50 minutes--probably a bad lecturer should quit after two minutes.

Beal: In a class we have students with many levels of motivation. Would not this affect the student's gain from a discussion just as well as the lecture.

Gage: That's true. At least the discussion method offers some possibility for action whereas in the lecture system you don't even become aware of the fact that his motivation is lagging.

Beal: What if his motivation is such that you can't get him to participate?

Gage: I try to get him into conversation to ascertain what the real cause is--through individual conferences. Of course with 60 or 100 students this is hardly possible. Research on class size has not given satisfactory data. They compared 300 students vs. sections of 30 with no significant differences. The outcome that you can get from this comparison is not what can easily be shown by multiple choice answers which they used.

Beal: The blanket statement that discussion is better in all types of courses is hardly justified.

Gage: The burden of proof is on the person who lectures. Samuel Johnson insisted that there was no reason to tell them when it's already printed--hand it out and have them read it. Until we develop answers to this argument the burden of proof is on the lecturer.

Bliss: How effective are visual aids in the presentation of subject matter?

Gage: Generally they are very effective. Films and television are used. They are beginning to develop ways of feedback from student to the teacher who televises. The main problem is that visual aids allow only for one way communication. In the laboratory these have obvious advantage.

Tyler: I would attempt to answer Samuel Johnson's statement--assign home reading. Education professors commonly tell us

that the discussion method is superior yet I know of no one who has consistently used it. We often confuse the problems between teaching science and general education. The subject matter is different and the approach must be different. Some of the burden of proof should be on the education men to show us how discussion can effectively present certain phases of scientific work.

Gage: Time magazine--latest issue--has a review of the lecture method as presented in India. Canned summaries are purchased to cram for exams--this is not good education. You can't compare the advantages of the discussion method with what is accomplished by lecturing, they're so much greater.

Zopf: Dr. Gage, do you feel that if we had distributed copies of your lecture before you began today, that it would have precipitated the number and interest in questions that you have had today?

Gage: An astute question. Whether there is more interest generated by the printed page than by an oral presentation. As for this presentation--Does a typical college lecture have the content of this talk or lead to a discussion of this kind?

Brady: We have a dual situation. We have students, and we have 75% of the people that populate our Universities. The approach should be quite different in teaching the two groups.

Gage: Many factors besides teaching methods govern our effectiveness--quality of the students we teach is certainly important; nature of the subject method has much to do. You can't discuss calculus as easily as you can sociology. Size of class, traditions of the institution, several other things-- all enter into the type of teaching method that will be most effective. Broad generalizations here are hazardous like any generalizations.

O'Connell: Reference has been made to a situation where students were discouraged from taking notes during a lecture-demonstration since they were required to have read the material before coming to class. Have any studies been made concerning this method?

Gage: Not that I know of--an intelligent guess is that note-taking helps in their catching and remembering. Passively

sitting there, doing nothing, they don't get much; taking notes they get more; taking active part in a discussion they get even more. Note taking as an activity does pay off to an extent.

Smolenski: Thus far emphasis has been put on the teacher. I feel that education is learning. The burden sould be placed on the student. Have studies been made to determine if the students work up to their capacity at the University level.

Gage: Studies of effectiveness show that the teacher makes little difference in the accomplishments of the students-- There is much greater correlation between student's ability and student accomplishment.

ECONOMICS OF DRUG PLANT PRODUCTION

Ralph F. Voigt

Industry, regardless of its products, is directly or indirectly concerned with economics. Some industries place more emphasis upon certain economic principles than do others. Processes that are peculiar to an industry will require a different economic consideration than that of another industry. In some areas it may be difficult to foresee the application of some economic principles. Regardless of the approach, each area of production is continually faced with problems involving the fundamentals of economics.

In drug plant production, one is immediately concerned about the sources of plant material, either from wild or cultivated plants. Necessary manpower, finances and essential equipment are directly important to operating a continuous and productive program in such an industry. Certain procedures peculiar to drug plants must be observed particularly in the growing of plants, as well as the collection, harvesting, drying, preservation and storage of the raw materials. Each of these special processes involves many factors which, if interrupted or altered, will affect the quality of the finished product. Obviously, this affects production and is directly concerned with the overall economy of the industry. The basic principles of commerce and marketing that have a direct influence upon the success of this industry govern the utilization of drug plants and/or their products. Processing of the raw material into products that are marketable and usable will certainly affect their consumption. Finally, research is an important factor in all of the phases of this industry as it is in any other development.

The following is an outline of the factors which directly or indirectly affect the economics of drug plant production. One may alter the significance of the major phases according to his knowledge and practical experience. Admittedly, one can add many details to each category. The outline is designed to serve as a guide or a starting point for the teacher who plans to develop the topic. On the other hand, a teacher may wish to develop only one phase of the overall subject. It is certain that the teacher will experience a responsive audience when the commercial phases of drug plant production are considered. The use of specific case histories, statistics, costs and prices will illustrate the basic economic principles as

applied to drug plant production and at the same time it will prompt the student to realize the importance of the industry. Additional information pertinent to the above interests may be obtained from such periodicals as the New York Journal of Commerce; Oil, Paint and Drug Reporter and The Foreign Commerce Weekly.

I. Source of Plant Drugs

A. Wild or Natural Growing Plants
1. Advantages
2. Disadvantages
3. Distribution

B. Cultivated Plants
1. Advantages
a. Control of botanical source and purity
b. Superior quality
(1) By plant breeding
(2) Control of Disease
(3) Proper harvesting
(4) Proper drying and storage
2. Disadvantages
a. Cost, increase
b. Labor, etc.
3. Distribution
a. Subject to alteration - depending on factors

II. Manpower

A. Labor
1. Unskilled
a. Individual
b. Organized - Unions
2. Skilled
a. Individual
b. Organized - Unions
3. Strikes
a. Effect on individual
b. Effect on economy

B. Management
1. Individual - Owner
2. Company
a. Foreman

II. (Cont'd)

b. Superintendent
c. Research Director
d. Officers
e. Board of Directors
f. Stockholders
g. Salesmen

C. Sociological Factors Affecting Manpower
1. Standards of Living
a. Homes
(1) Location
(2) Tenants
Owners
b. Food
(1) Quality
(2) Availability
2. Nationalities
a. Language
3. Races
4. Religion
a. Superstitions
5. Finances
a. Steady Income
b. Intermittent - Seasonal
c. Retirement
d. Insurances
(1) Hospital
(2) Medical
(3) Life
(4) Endowment
(5) Accident
6. Diversions
a. Recreation
b. Travel
c. Sports
d. Hobbies
7. Government
a. Taxes
b. Price Controls
8. Organizations
a. Social
b. Business or Professional

III. Finances

A. Monetary Values
   1. Dollar Value
   2. Inflation
   3. Currency Values
   4. Exchange
      a. Domestic
      b. Foreign

B. Costs
   1. Labor
   2. Supplies
   3. Equipment

C. Investments
   1. Capital
   2. Real Estate
   3. Equipment

D. Dividends

E. Interest

F. Taxation
   1. Income
   2. Corporation
   3. Real Estate
   4. Licenses

G. Revenues, Other

IV. Equipment

A. Hand
   1. Gardening Tools
   2. Harvesting Tools
   3. Sprayer

B. Mechanical
   1. Special Devices for
      a. Seeding
      b. Transplanting
      c. Cultivating
      d. Cutting
      e. Harvesting
      f. Drying

IV. (Cont'd)

g. Packaging
h. Storage
2. Processing Equipment
a. Percolators
b. Stills
c. Presses
d. Evaporators
3. Communication
4. Transportation
5. Office Equipment

V. Plant Growth

A. Natural Growing Drug Plants
1. Distribution
2. Ecology
3. Geography
a. Elements of Climate
(1) Air temperature
(2) Atmospheric pressure and winds
(3) Altitude
(4) Atmospheric moisture and precipitation
(5) Air masses, fronts and atmospheric disturbances
(6) Light
b. Humid Climate
c. Dry Climate
d. Climatic Regions
(1) Temperate
(2) Subtropical
(3) Tropical
e. Elements and Types of Terrains
(1) Slope, Surface, Arrangement Dimensions
(2) Plains, hills, mountains
f. Forests, Deserts
g. Seas
h. Water Resources
i. Soils
(1) Distribution
(2) Conservation
j. Population
k. Settlements
l. Agriculture
Types of

V. (Cont'd)

m. Natural Vegetation and Associated Animal Life

4. Labor

B. Cultivated Drug Plants

1. Propagation from Seed
   a. Preparation of Seed Bed
   b. Seeding (Greenhouse)
   c. Transplanting
2. Vegetative Propagation
   a. Division
   b. Layerage
   c. Cuttage
   d. Grafting
3. Weed Control
4. Insect Control
5. Disease Control
6. Climate

Factors Affecting Propagation
(See preceding outline under geography)

7. Soil
   a. Physical Nature
   b. Topography
   c. Fertility
   d. Management
      (1) Cultivation
      (2) Fertilization, Fertilizers
      (3) Irrigation
   e. Maintenance
8. Labor
9. Investment
   a. Fquipment

VI. Collection, Harvesting

A. Wild Plants vs. Cultivated Plants

B. Proper time - Influence on Quality

1. Roots, rhizome & Barks
2. Leaves
3. Flowers
4. Fruits
5. Seeds

VI. (Cont'd)

C. Mode of Harvesting
   1. Hand
   2. Machine

D. Labor

E. Investment
   1. Equipment

VII. Drying

A. Air Drying

B. Sun Drying

C. Shade Drying

D. Artificial Heat

Special Procedures According to Nature of Drug

E. Labor

F. Investment

VIII. Preservation, Storage

A. Garbling

B. Packaging

C. Storage requirement
   Special Conditions

D. Insect Attack

E. Temperature

F. Moisture

G. Deterioration

H. Labor

I. Investment

IX. Commerce, Marketing

A. Supply and Demand

B. Production
   1. Domestic
   2. Abroad
   3. Shift in Centers of
   4. Fluctuation in Amount
      (Seasonal Patterns)
   5. Range of Products

C. Trade
   1. Communication
   2. Transportation
   3. Organizations
   4. Imports
   5. Exports
   6. Barriers
      a. Competition
      b. Embargoes
   7. Ports

D. Climate

E. Government
   1. Agencies
   2. Controls
      a. Licensing
      b. Patents
      c. Trademarks
   3. Tariffs
   4. Politics

F. Finances
   1. Investments
   2. Credit Terms
   3. Insurances
   4. Economics of Country

G. Conflicts

H. Manpower

I. Sales
   1. Personnel

IX. (Cont'd)

2. Product Promotion
   a. Advertising
   b. Fairs, Exhibitions
3. Trade Organizations

X. Processing

A. Products

B. Methods

C. Equipment

D. Investment

XI. Marketability, Utilization, Consumption of Products

A. Quality of Product
   1. Identity
   2. Purity
   3. Evaluation - Assay
      a. Physical
      b. Chemical
      c. Biological
   4. Adulteration

B. Quantity Available - Supply
   1. Source
   2. Manpower
   3. Finances
   4. Investment

C. Demand - Uses
   1. New & Old Therapies
   2. Change in Therapy
   3. Rate of Use

D. Price
   1. Supply
   2. Surplus
   3. Financial Status
   4. Interest

XI. (Cont'd)

E. Economic Developments
   1. Living Conditions
      (See Sociological Factors)
   2. Natural Resources
   3. Industry
      a. Manufacturing
      b. Construction
   4. Government
      a. Controls
      b. International Transactions
   5. Exports - Imports - Foreign Trade
   6. Transportation
   7. Communication

XII. Research

A. Personnel

B. Areas

C. Facilities

D. Cost

E. Results

DISCUSSION

Tyler: Do you know of a single strictly medicinal plant that can be cultivated in the U.S.A. that can be economically placed on the world market?

Voigt: None, other than Rhamnus purshiana.

Tyler: I mean in cultivation.

Voigt: Are you not really cultivating Cascara?

Question: Which drugs are cultivated in the U.S.A.?

Woodward: The mints, Peppermint, Spearmint. A strictly medicinal plant--Digitalis is the only plant that penny for

penny is economically feasible for cultivation in any quantity in the U.S.

Simonian: There was no mention in your talk of monopolies or concessions and controls of that type. When one attempts to buy in the near East he finds that he cannot import without reselling and rebuying through the proper channels.

Call: I have made some interesting observations. The problems I have encountered were that unqualified people were my competitors. They were not interested in quality, e.g., separating weeds, in fact they didn't even care if they had the correct species. They openly claimed that they would get by with anything they can. The minute you attempt to collect crude drugs you become the subject of suspicion--everyone in the area is watching you. They often report to the F.B.I. that you may well be collecting narcotics on the side. They try to find your shippers, then report to their people who in turn write them to undersell you. The uncertainty of the market is also a great problem. The qualified person is not recognized by buyers or competitors.

Sciuchetti: To an extent research has helped to solve these problems. In the peppermint area of the Lambeth valley concerted work has been done on the improvement of the stills to fight foreign competition; to do a more efficient job of agriculture; to get better harvests and produce a better product. Each phase of the problem of production was given serious thought. Unless we use such methods we can't hope to compete with the European market.

Dunn: Do we have any taxes on importation of foreign crude drugs to protect our own interest?

Woodward: Most crude drugs are imported free of duty except for a few. The cost of collecting the tax is greater than the tax itself, e.g., for sweet orange peel, the tax is ½¢ per pound; on extracts it is 5% ; on balsams it varies from 5% to 7½%, alkaloids from 5% to 10%. Most of the duties have been cut in half within the past ten years. There isn't much protection through duty, really. One may not assume that even a 10% tax is going to greatly deter the importation of Balsam of Peru.

Dunn: What is the underlying reason then for the duty?

Woodward: Our government originally believed that the proper management of this country should be characterized by frugality. The balance of income and outgo of money should be in the black. They got along on very little money and made quite a lot from import duties, just as duties between the states was important. Then an income tax was introduced and subsequently the relationships of these taxes and duties changed widely. At present, things have changed to the point that it would be simpler if these duties were dropped altogether.

Koffler: In your experience with drug plants can you recommend any drug plant that people can grow now to make additional income at their own home property?

Voigt: I get such questions weekly. I commonly tell them, "Don't start unless you are prepared to cope with all of the problems mentioned in the outline given today.

COMMERCE IN NATURAL DRUGS

E. F. Woodward

If you want a pair of figures to ponder - The U. S. Imports of Botanical Drugs etc. last year amounted to about $10,000,000, whereas the sales of finished Reserpine products alone amounted to $30,000,000. Those two figures explain a good bit about the industry. It's a long way from Rauwolfia Root to Reserpine tablets and a long way from the days of trading in Snake Root until today's integrated exploration - procurement - processing - purification - Food & Drug Master Files - Customer Servicing - inventory position type of business.

More numbers - Granted the number of crude drugs in the USP is decreasing we should still remember that such drugs as Cortisone have come into the USP, drugs derived from the steroids obtained from Dioscoreas. The imports of these steroids from Mexico went from $300,000 in 1948 to over $3,000,000 in 1957. This is an increase of 10 times in 10 years.

As for commerce in the "old reliables" let me list a few that are still definitely important and in useful demand: -

USP drugs	NF drugs
Aloes	Ergot
Belladonna	Hydrastis
Cascara	Senega
Digitalis	Senna
Ipecac	
Opium	
Podophyllum	

Probably you are aware of one trend - a botanical that formerly appeared in many proprietary and ethical preparations, official formulae and prescriptions, too, is now frequently found in only one or two branded products. The number of preparations of the botanical in question may have diminished, but the total quantity used may well have increased. Take Buckthorn Bark -- there are only two major users in the U. S. - but the tonnage is quite considerable.

Another development is that there are a number of drugs of botanical origin that are derived from materials that are not botanical drugs in themselves. For example - Atropine and

other mydriatic alkaloids are now obtained from the Duboisias, Rutin is obtained from Eucalyptus macroryrcha, Khellin is obtained from Ammi visnaga seed, and there is the whole list of steroids elaborated from the Dioscorea sapogenins.

Right here it might be a good place to suggest that the province of the pharmacognocist could - in fact does - go beyond the Materia Medica. There is that group of materials referred to so aptly by the British as "M.F.P."--Minor Forest Produce. Such things as timber, rubber fibres, edible nuts and oil seeds are not excluded. Included, are a variety of botanicals of economic value nevertheless -- products of present or former use in medicine, and products of all sorts of other uses.

There are a number of drugs that have diminished in drug use but are still important in other fields. For example Quassin is very important in the denaturing of alcohol. Agar is important to the baking industry. Saponin from Soap Bark is important to the photographic industry.

What person is better trained and more widely experienced to deal with these materials, investigate them, and exploit them? Interesting flavors and odors. Gums and resins. Food and fabric dyes and colors. Foaming agents. Cosmetic materials. Insecticides.

I suggest that a well trained and well rounded pharmacognocist can be more than a jump ahead of the botany-trained economic botanist, or the chemistry-trained phytochemist. We have much to contribute - if we only are willing to open our sights.

The days of drug trading on Front Street in New York and in Mincing Lane in London are gone. Manufacturers don't want to be concerned with bales of roots and barks. The patient doesn't want to swallow a muddy mixture of tinctures and powders.

The manufacturer wants an extract or an alkaloid - something much more convenient to use and of more definite, standardized composition. The days of merchant trading have been replaced by competent and reliable manufacture, in elaborate equipment under technically controlled production procedures.

It is true that more Alkaloids are coming in from Europe just as is the case with Vitamins. This is mainly due to the low cost of highly skilled labor in Europe, and in Japan too.

But this is not particularly the case with Extracts because some of them are still uncharacterizable and the products of domestic manufacture are still preferred because of their reliability.

You could turn out a green extract that looks for all the world like Solid Extract of Belladonna Leaves but was in fact made from a "Solid Extract of Mattress Covers" plus a selection of alkaloids and some chlorophyll. And no known procedure could readily differentiate or prove that it is or it is not what it seems to be.

You could make an Extract of Cascara where the yield is 2 to 1 versus 4 to 1, but you'd be ashamed to put your label on it. This is one reason for the need for more stringent tests and more useable standards. In the case of cascara, the Penick Casanthranol Assay is suggested as a step forward.

As for drug cultivation in the U. S. it is decreasing except in times of emergency. About all that remains are a few fields of:

DIGITALIS
BELLADONNA
HYDRASTIS
WORMSEED
ERGOT
THE MINTS
and some GINSENG.

There is more of drug plant cultivation in foreign countries. Belgium does a nice job, as does England, France, Holland, Russia and India, to name but a few. But most drugs are still obtained from wild growing plants.

The major crops cultivated abroad include:

OPIUM
PSYLLIUM
ERGOT
PAPAIN
SENNA
STRAMONIUM
HENBANE
PEPPERMINT
CINCHONA

Trials are still under way on a number of drugs including the Dioscoreas in the U. S. and Puerto Rico, and Ipecac in India and Central America.

Perhaps the most important development in the last 10 years - and it has been that long - is renewed interest in botanical drugs, some of the old ones, but especially some of the new ones.

True, there's no commerce yet in many of them, but the present research activity is certain to effect the commerce within the next few years.

Practically every large pharmaceutical company has a project on screening new botanical drugs or they are paying attention to botanical drugs within the scope of their research projects which may be set up differently, such as on a disease-goal basis.

Perhaps it all stems back to the time of World War II when there was a frantic search for a substitute for the Javanese Cinchona Barks. This substitute was found in Totaquine derived from South American and Central American Barks. Then Totaquine was replaced by synthetic antimalarials. This started many countries searching their own backyards for valuable plants both for such things as rubber and for medicines. The search in Australia yielded the Duboisias. The search in India yielded Rauwolfia. It was as these countries began to feel the pinch of economies, and as they were spurred by nationalism, that they began to investigate and re-investigate their own materials. Still another push was given by the Dioscoreas and another surge of interest came from some of the more interesting drugs still being discovered in the Apocynaceae.

It would be difficult to list an exception - a pharmaceutical company not interested in botanical drugs; whereas 10 years ago the companies continued to use some botanicals on a declining basis, <u>but seldom was there a pound destined for research</u>.

And there are many Government and Institutional programs going on in India, Pakistan, Burma, Red China, Russia, Australia, Egypt and here in the United States. The Bethesda anti-cancer drug search, the U.S.D.A. search for steroid bearing plants, and the search for lower and higher plants yielding antibiotic substances all are well known, continuing efforts.

Perhaps you are aware of the publicity and public interest in this turn of events. Recent articles have appeared in all

sorts of publications including the New York Times, Time Magazine, The Wall Street Journal, Cosmopolitan Magazine and I understand that there are soon to be articles in Popular Mechanics Magazine and in the Baltimore Sunday Sun.

Even Francis Chilson had an item in his column in the July issue of Drug and Cosmetic Industry. Then there's the increased interest on an adacemic level as exemplified by the new graduate course in Pharmacognosy at the University of Michigan under Professors Deno and Paul, and by the interest shown in reorganizing our group as the American Society of Pharmacognosy.

What can we hope to find? Certainly some presently unknown plant constituents - useful in themselves or in the Materia Medica, or as starting raw materials for elaboration. And I hope the elaboration isn't all credited to the synthetic organic chemist. Certainly the route from Diosgenin to Cortisone is not all under chemical guide posts as the start was certainly in Botany and Pharmacognosy.

A word about availability. I don't think we should hesitate to search for, and investigate a drug, on the basis of assured supply. Find the drug first then see if you can get enough from wild collections. If not, look to cultivation, if not, look to allied species. In the case of the Rauwolfia's we know how important allied species can become. A work of caution - a lesson learned from the Strophanthus search - it is important to be sure of the identity from the start. Pharmacognosy can be described as the Botany, Chemistry and pharmacy of plants, and we should not forget to do the Botany part first.

I hesitate to risk inferring that this middle century period will be known as the "Pharmacognosy Age". Missiles - outer space and Rock and Roll will continue to receive more coverage. But as contrasted with the days of Berg, Tschirch, Hanbury and the many other famous men of over 100 years ago, Pharmacognosy could well be entering into another, very important, era.

DISCUSSION

Pokorny: Can you tell us roughly how many or how much of the obsolete drugs go into the non-pharmaceuticals such as bitters, Worcestershire sauce, etc.

Woodward: We do have considerable profitable sales for Asafoetida and tamarind which are used in Worcestershire sauce. We do know the formulae for several private patented preparations but these are not generally available on the public market.

Ramstad: In a survey I made through the literature on drugs I could not find a use for the drug Hydrastis. Can you tell me uses for this drug?

Woodward: The principal use of Hydrastis is in the preparation of Murine and a well known douche powder. There are quite a number of preparations intended to be used on mucosa, eye, mouth, nasal, etc.

Pokorny: What information have you about drugs obtained from the sea?

Woodward: Algae are used in the preparation of algins, alginates, the principal use of these is in the dairy and related food industries, smoothing out of ice-creams, puddings, cake mixes, etc. Our company handles very little of it.

Dunn: Do you get any drugs out of Red China?

Woodward: We get no drugs out of Red China directly or via other ports.

Dunn: Does this cover Russia also?

Woodward: No--only Red China, Viet Nam, and a couple smaller ones in the same area.

Beal: What is the commercial production of Castor Oil?

Woodward: Production of castor beans is carried on in tropical areas. Most of the market is for lubrication in jet engines.

Beal: I know of farmers in Missouri and Arkansas who grew the plants for use but this appears to be discouraged by our government.

Woodward: I would anticipate that the government departments involved would be interested in having a few such operations in this country as a stopgap in case of serious problems in importing, though most of the supply is imported from tropical areas.

Roscoe: There is renewed interest in production of Castor Beans in the area around Bakersfield, California. They have developed a machine that strips 90% of the fruits without badly crushing seeds which appears to be very effective.

Woodward: If you should ask a company, e.g., Allis Chalmers to design a machine for this purpose--if your budget is sufficiently large they'll produce an effective machine. If it is small they won't show particular interest.

Sciuchetti: Does your company get most of their drugs from Europe, and do you grow many in the U.S.A. yourselves?

Woodward: We cultivate some plants, principally Digitalis.

Eby: How about Cascara sagrada supplies?

Woodward: The supply was short this year. It was brought in from sawmills wet due to rain and poor prices were offered. The supply is relatively short, consequently the price is 30% higher this year.

Bienfang: In reading the literature on Rauwolfia, I saw the statement that the alkaloids are present in the alceroxylon fraction. I don't know the meaning of the term.

Woodward: The term means "weakly basic" in contrast to strongly basic or alkaline.

Tyler: When I left Washington the Cascara supply was high; prices were good; the outlook was excellent.

Woodward: This was true a month ago. The picture has changed drastically since then.

Martin: Can you comment on Guar gum?

Woodward: Most of the work done on Guar gum was done by General Mills. A breakthrough was made by Wallenstein Nichols who worked on starches prepared in the food industry.

This gum was discussed at length at the Plant Science Seminar of 1957. The chief source of Guar gum at this time is West Pakistan.

RECENT ADVANCES IN THE STUDY OF ANATOMY AND HISTOLOGY OF DRUG PLANTS

Heber W. Youngken, Sr.

Among the foreign contributors to these advances within recent years and the work which they accomplished, the following appear to be outstanding:

Sarking, Kiss, Danei and Riedel in "Acta Botanica Hungaricae" 5(1-2):97-202, 1959 have reported on "Studies of Papaver somniferum L. and selection trials of poppy varieties for increased morphine and seed production. They describe the crop ecology of Papaver somniferum and illustrate the seeds, seedlings, leaves and stages in the development of the plant and flower. Line drawings detailing the morphology of the flowers of 4 morphine-producing plants are illustrated in color. The histology and cytology of the pistil and several types of mature ovaries are pictured. Seven subspecies and 43 varieties of P. somniferum are recognized.

In a series of 6 parts which appeared in volumes 7-10 of "Journal of Pharmacy and Pharmacology" under the title, "The Pharmacognosy of Aspidosperma Barks of British Guiana", G.E. Trease of The University of Nottingham and his associates, J.D. Kulkarni and J.M. Rowson, have described and illustrated in detail the barks of 6 species of Aspidosperma, namely, A. ulei, A. excelsum, A. album, A. megalocarpum, A. quebracho-blanco, and A. oblongum. They found all of them to have a common pattern of morphology and anatomy. All occur in thick and flat, curved and channeled pieces; the cork is abundant, furrowed or fissured externally and bears epiphytic lichens or liverworts; the inner surface of each is longitudinally striated; the fracture is either short, granular and splintery in the outer part and fibrous in the inner part or it is very hard. The odor of each bark is indistinct and the taste is bitter and aromatic.

P.K. Sanyal and T.E. Wallis of the University of London have investigated the anatomy of Valeriana officinalis L. rhizome, roots and stolon, and the polyploid forms of this species. The development of lacunae in the pith of the rhizomes is shown to originate from cells having no visible contents by their multiplication and breakdown. The occurrence of sclereids in the pith of the rhizome is shown to be

characteristic of the tetraploid plant. J. Pharm. Pharmacol. 0 (1957) 162-175.

The same workers have found that the starch grains of roots of tetraploid plants have a maximum size of 18μ while those of roots of octoploid plants have a maximum size of 30μ.

R.M. Ridgway and J.M. Rowson of the University of London have reported in detail their observations on the structure of Glinus oppositifolius roots which has occurred on the market as a substitute for Senega. The differential characters between this substitute and Polygala Senega are given. The transverse section of the Glinus root differs markedly in the distribution of xylem and phloem tissues. Oily droplets are absent in the parenchyma cells of Glinus but present in these cells of Senega. Unlike the parenchyma cells of Senega, those of Glinus contain small, simple and 2-to 6-compound starch grains. J. Pharm. Pharmacol. 8(1956) 915-926.

W.E. Court, W.C. Evans and G.E. Trease of the College of Pharmacy of the University of Nottingham have reported their investigation of "The Structure of the Root and Stem of Rauwolfia caffra Sond". The structure of the root is stated to closely resemble that of Rauwolfia vomitoria, the chief distinction being the absence of alternating lignified and nonlignified cork cells in the cross section of R. caffra. J. Pharm. and Pharmacol. 9 (1957) 237-249.

R.R. Fell and J.M. Rowson have reported their studies on the "Anatomy of the Leaf of Rubus idaeus L.", J. Pharm. and Pharmacol. 8 (1956) and "The Anatomy of the Leaf of Rubus fruticosus L., J. Pharm. and Pharmacol. 9 (1957) 295-310.

T.A.N. deToledo and A.S. Grotta of the University of Sao Paulo, in a pharmacognostical description of the root of Rauwolfia Sellowii Muell. et Argov., have described and illustrated the macroscopic and microscopic characteristics of the root. Anais da Faculdad de Farmacia e Odontology da University Sao Paulo 13 (1955) 41-48.

Roberto Wasicky of the same University has described and illustrated the gross anatomy and histology of the stem, leaves and flower of Deianira nervosa Cham. et Schlecht., family Gentianaceae, a bitter herb of Braxil which has been used as a substitute for Centaurium umbellatum. Anais da Faculdad de Farmacia e Odontology, University Sao Paulo.

M. Felklova and K. Babkova of the Pharmacy Faculty of Bruenn, Czechoslovakia have reported the results of "Anatomical Studies on Laticiferous Vessels of Papaver somniferum L. during the Vegetative Period". They studied the living latex ducts in all organ sections **which were stained with Sudan III.** The greatest number of latex ducts and highest morphine content occurred in the capsules. Pharmazie 13 (4) 220-229, 1958.

Among the workers in India, the following investigations may be cited:

S. Prasad and K.C.Gupta of Banaras Hindu University, in a paper entitled "Pharmacognostical Studies of Andrographia paniculata Nees," have reported the results of their studies of the macroscopic and microscopic structure of the stem, leaf and floral parts of this Asiatic species. Their paper is illustrated with 40 figures. Ind. J. Pharm. 19 (1957) 163-170.

P.N. Mehra and J.E. Bkalnagai, in a paper, "A Comparative Study of Satawar and Its Supposed Botanical Source", have described the histological characteristics of this root drug and compared it with the root of Asparagus racemosus. A. racemosus was found not to be the Indian root drug Satawar. Ind. J. Pharm. 20 (1958) 33-39.

C.S. Shah and L.P. Aghara have reported on the macroscopic and microscopic structure of Tuticorin Yellow Root, a substitute for Senega and compared these with Glinus oppositifolium. Ind. J. Pharm 20 (1958) 292.

S. Prasad and L.P. Aghara, in a well illustrated paper, have reported on the microscopic characteristics of the stem and root of Aristolochia indica L. "Pharmacognostical Studies on Aristolochia indica L.", Ind. J. Pharm. 20 (1958) 285-292.

In the United States research in the anatomy and histology of medicinal plants continues its advance, although in recent years the number of American workers in this field has decreased.

Considerable new information has been disclosed as the result of the publication of a series of researches carried out in 1958-59 on the morphology of species of the genus Thymus by Ikram Hassan and Marin S. Dunn of the Philadelphia College of Pharmacy and Science. These have been combined in a book entitled "Studies of the Genus Thymus (In 10 Parts)". Part 1 contains a comparison of the diagnostic characteristics

of Thymus vulgaris L. and Thymus Serpyllum L.; Part 2, the palisade numbers of leaves usually located on branches of T. Serpyllum particularly its varieties albus and coccineus; Part 3, a comparison of the diagnostic characteristics of T. Chamaedrys Fries and T. Herba-barona Loisel; Part 4, compares the diagnostic microscopical characteristics of T. capitatus Hoffmgg and Link and T. striatus Vahl.; Part 5, discusses the diagnostic characteristics of T. carnosus Boiss. in comparison with those of T. villosus L.; Part 6, a comparison of the diagnostic microscopical characteristics of T. hirsutus Bieb and T. heterotrichus Griseb.; Part 7, a comparison of the diagnostic microscopical characteristics of T. pectinatus Fisch. and T. Zygis L.; Part 8, gives a comparison of the floral leaves and calyces of various species of Thymus; Part 9, tabulated histological data for certain Thymus species; Part 10, a histological key for the identification of certain Thymus species. Each part is well illustrated with line drawings.

A material advance has been made in our knowledge of the gross anatomy and histology of Ptelea trifoliata L., its subspecies and varieties, and the related species, P. aptera and P. crenulata by the extensive research carried out by Virginia L. Bailey of Wayne State University and very recently reported in a well illustrated paper entitled "Studies in The Genus Ptelea". Her paper was submitted to the Edwin L. Newcomb Memorial Award in the Teacher-Research Worker group this year.

Heber W. Youngken, Sr. has contributed a paper under the title "A Study of The Root of Morinda citrifolia L.I" in which he described the plant, the physical characteristics of the root and of the commercial drug, the histology of the root and the powdered root. Jour. A. Ph. A., Sci. Ed., 43 (1958) 163-165. A second paper in which the anatomical characteristics of the stem of Morinda citrifolia are described by the same author is scheduled for presentation at this month's meeting of the scientific section of the A. Ph. A.

In a book entitled, "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology" published by Little, Brown & Co., Boston, in 1957, R.E. Woodson, Jr. of The Missouri Botanical Garden has discussed the systematic anatomy of a number of Rauwolfia species and H.W. Youngken, Sr. has discussed the detailed morphology and histology of Rauwolfia serpentina, R. canescens of India, R. heterophyla of the western hemisphere, R. vomitoria, R. micrantha, R. perakensis, R. Beddomei, and R. cambodiana. Numerous illustrations accompany the descriptions.

Mr. Philip A. Babcock completed his work at the Massachusetts College of Pharmacy for the degree of master of science in June of this year. His research dealt with "The Histology of Three South American Crude Drugs of Plant Origin". The drugs were:-

Stem of Aristolochia triangularis Chamisso (Aristolochiaceae)
Bark of Casearia sylvestris Swartz (Flacourtiaceae)
Leaf of Schinopsis balansae (Anacardiaceae). The detailed histologies are considered.

In a paper presented this year to the E.L. Newcomb Memorial Awards Committee of the A.F.f.P.Ed., entitled "A Comparative Pharmacognostical and Phytochemical Study of Solidago juncea Ait., Solidago canadensis L. and Solidago graminaefolia Salisb. David Silverberg and Richard L. Hogg, students at the Ferris Institute College of Pharmacy, described and illustrated the gross morphological and histological characteristics of these plants. They found it possible to differentiate these species by the histological characteristics of their leaves, particularly by the location and type of glandular and nonglandular hairs.

Charles J. Hillson of the Dept. of Botany and Plant Pathology of Pennsylnania State University has recently published a paper on "Comparative Studies of Floral Morphology in the Labiatae". In this report of his research a number of flowers of drug genera are considered.

Magdalena Cantoria has recently published her master's thesis on "Studies on Rauwolfia vomitoria Root". It contains many line drawings on histological elements observed.

DISCUSSION

Question: Do you know of anyone who has done any work on comparison of the histology of hybrid plants with their parent plants?

Youngken: Yes, I ran across several examples of these, you can find these in Biological Abstracts within the past one or two years.

Dunn: Have you found any references on comparative features on any species of Lavender?

Youngken: I don't recall anything of comparative nature in that genus. Older work was largely taxonomic rather than morphological.

Ramstad: Have you come across any study dealing with environmental changes having an effect on anatomy of the plant involved.

Youngken: Only when the environment is responsive over a period of time in producing form, which inevitably differs from the pure species.

Martin: Edgar Anderson has attempted to reduce this type of thing to a statistical analysis of environmental features. We have found that you can characterize an area and plot the statistical value of plants found in that area as compared with others at a lower area from Appalachians to the Louisiana Flood Plain---plot the same species in that area and find variations that are due to environmental effects.

RECENT ADVANCES IN PLANT MICROCHEMISTRY

Gunnar Gjerstad

As this report is being written, the results of the 1959 questionnaires on current pharmacognosy teaching are not available. Vanderwyck's report of 1953 (1), indicates a wide diversity of laboratory work.

It is my impression, however, from perusal of presently widely used laboratory manuals that the trend in recent years has been away from macroidentification of biological drugs towards micro-morphology, and chemical identity and purity tests. These topics together with those of plant extraction of the active principle and chromatographic separations and identification of the active principle, constitute, in my opinion, a step in the right direction. After all, we do not use drugs because they represent a certain phylum, genus, species, family, or any plant part, but because they contain an active medicinal ingredient.

The microchemical study of plants in its classical sense was elaborated particularly by Tunmann and Rosenthaler (2) who emphasized the use of a microscope for the study of crystalline precipitates.

Today, the term microchemistry does not necessarily involve the aid of a microscope, but is rather defined as "chemistry concerned with minute or microscopic objects or quantities." Partition chromatographical analyses are without doubt among the most useful tools in modern plant chemistry. Since this area will be discussed in a later paper, I shall here limit my presentation to other types of microchemical analyses.

All of us surely have included microchemical methods in our undergraduate teaching when staining morphological sections with phloroglucinol-HCl to test for lignified tissues, color reactions for mg. quantities of various alkaloids, precipitation of the sulfates of hydrastine-berberine, and the thalleoquin test. Microchemical methods are in the vogue today. Their advantages over conventional method are apparent: economy of time, material, and energy. Two objections have been raised against micro-analysis: initial expense of apparatus and the danger the mg. samples of larger amounts of test material cannot become as representative as those used in the older macro-

analyses. This may be corrected, however, by thorough homogenization of substances under testing, and careful sampling.

Annually, in the April issue, there appears in "Analytical Chemistry" (3) review articles of the various fields of microchemistry, including such topics as organic, inorganic, physical chemistry, and of pharmaceutical micro-analysis. These are basically concerned with elemental analyses and functional group determinations with submicro quantities, where several elements now may be determined simultaneously, in impressively short time (½ hour or less) and evidently with remarkable accuracy. Since this type of analysis is of lesser interest in pharmacognosy teaching, I am just referring to them in passing, since they are very useful in research.

The conventional type of plant micro-chemistry, according to Bräutigam, (3e) has not been as attractive to researchers in this country during the past decade, in spite of newer microscopic designs with attachments for fusion, interference (thickness measurement), phase (diaphragm), ultraviolet, fluorescence and infrared studies.

Current apparatus, useful in microchemistry, have been illustrated and explained in the more recent textbooks, and not many startling new devices have appeared except that Lüdy-Tenger in 1947 designed a so-called "T.B. Block" (T.B. for Technikum-Burgdorf), which is largely a versatile modification of Koffler's micro-melting point apparatus and which may be used also for micro-sublimation carried out in one step on the microscope stage, and for photomicrography. In this paper (4), micro-sublimates of Cantharis, Rhubarb, Uva ursi and Cola nut have been given and their sublimates are illustrated. This apparatus has the advantage over current methods that the characteristic sublimation <u>temperature</u> may be determined, thus aiding in the identification. In this same device, iodine values may easily be determined on a microscale as follows: .1 Gm. (2 drops) of oil is weighed accurately on a micro slide, then exposed to bromine vapor for one hour, further heated on the micro slide for two hours to 60° in order to remove excess of bromine. After cooling, the slide is weighed again and the amount of chemically bound bromine determined, and I. V. calculated. This method is reported to be very accurate.

Another beautifully illustrated paper by the same author (5) is concerned with the micro-precipitation of penicillin with various bases. However, the performed experiments are

rather limited considering the extensive available literature on Penicillin. Thirty-seven known plant bases, most of them alkaloids, and twenty-two synthetic alkaline substances have been examined on precipitability with potassium Penicillin. The plant bases yielded only sporadic, amorphous precipitates. Among the synthetic alkaline substances, the following which were found to be suitable for microchemical identification, are listed in order of decreasing sensitivity: 1. N,N'-Dibenzylethylenediamine- hydrochloride, 2. Benzyl-beta-phenylethylamine-hydrochloride, 3. Procaine-hydrochloride, 4. Chloro-Procaine. The bases must first be buffered to pH 7 by means of sodium acetate.

The same author has done considerable work on the microchemistry of nicotinic acid (6). The potassium iodide-bismuth solution classically employed as so-called "BiJ reagent" is also suitable for identifying nicotinic acid as well as its amide. It is recommended to use for this purpose a "BiJ 1.5" reagent in which the HCl content is somewhat increased over the Dragendorff's strength. Nicotinic acid could be detected in Coramin (a mikethamide preparation) with as little as 15 drops of the substance.

Another work is concerned with the precipitation of alkaloids by potassium precipitating agents (7). Thirty-seven plant alkaloids (1% solutions) and eight synthetic bases were examined by means of nine of the best known potassium precipitating reagents. It was found in 400 performed reactions, that 193, or 47.7% produced precipitates; of these 28% were crystalline in nature. Some of these crystals can be used as an auxiliary microchemical tool for the identification of the alkaline substances. Sodium tetraphenylborate ("Kalignost") was found to be the only reagent suitable for quantitative determinations. In contrast to "Kalignost", sodium-salts of uranyl acetate and dioxy-tartaric acid do not produce precipitates with the exception that uranyl acetate precipitates berberine sulfate.

Sandri (8,9), working in Italy, has recently introduced various new complex alkaloid reagents consisting of relatively rare elements. Descriptions are given of several precipitates obtained with bromothallic acid and organic bases such as betaine, choline, nicotinic acid amide, etc. He claims to be able to distinguish the purine basis, such as caffeine, theobromine, and theophylline by means of this reagent. Bromoauric acid is proposed for the microchemical identification of alkaloids and certain organic bases, particularly pyridine and

quinoline homologues. Special interest attaches to the crystalline precipitates given by caffeine, theobromine and theophylline since they permit a differentiation of these bases.

Most of the reactions reported above require purified solutions of the test substance.

Coming closer to home, Ramstad (10) seems to be one of the few pharmacognocists in this country who has been doing classical microchemistry during the past decade. He did an extensive screening of plant materials for chelidonic acid. His procedure is astonishingly simple, very sensitive and specific, and is carried out as follows: A small piece of any plant organ for test is placed on a microslide, to which a few drops of 20% aqueous potassium hydroxide are added. Immediately, a yellow color is produced and after a few minutes, thin thread-like crystals precipitate out. These show a typical refraction of light and a dichroistic opalescence. The crystals disappear within one-half hour. Ramstad showed that a concentration of 5×10^{-5} M. could be detected. Of 1143 tested herbarium species representing 238 genera, 51% gave a positive reaction. (Chelidonic acid has indicentally later been shown by him to be a growth factor in plants).

If similar specific reactions could be found for all plant ingredients of interest to pharmacognocists, conventional plant extraction and even paper partition chromatography would prove by comparison to be more cumbersome and unnecessary for plant analysis. More work along this line is strongly indicated, although similar specific reactions in plant tissues may be difficult to design.

In our efforts to characterize and assay any crude drug by use of an analytical table whereby all official drugs could be analyzed qualitatively and quantitatively, some type of "push button" method has certainly been a dream of all of us. A systematic procedure along these lines was recently published by the Criminalistics Laboratory of the District Attorney's Office in San Jose, California (11). I am sure that some of you will be skeptical about this work after I have outlined it in some detail; so would I if this work had not been sponsored by a United States Public Health Service grant and evidently used to convict people of murder.

The systematic method permits the identification and determination of microgram quantities of organic compounds and poisons in biological drugs as well as specimens of blood,

liver, stomach contents, and urine; the latter analyses may be complicated by the background absorption given by the biological matter; hence additional purification and decoloration may be indicated in these cases.

Scheme of Separation

Gross liver samples and samples of stomach contents are extracted as customary for the isolation of organic drugs and poisons. The aqueous extract is evaporated, and the residue is used to prepare an aqueous solution promising a concentration of 100 to 500 ppm. of the active ingredient. One milliliter of this solution is submitted to systematic extraction followed by spectrophotometric investigation of the fractions.

As a general procedure, the following is recommended: One ml. of an aqueous extract of the unknown is buffered to pH 4.5 - 5, and extracted with a relatively large volume of chloroform. The latter is equilibrated with a small volume of aqueous NaOH. The pH of the aqueous layer is then raised to 8.0 and equilibrated with chloroform.

As you would expect, certain compounds will distribute themselves over two or more fractions, following the Nernst equation, or because of ionization or due to hydrolysis and other possible changes. However, according to this method all fractions must be analyzed in the Beckmann apparatus, and in the tables which follow, you will find some compounds are listed in more than one table and with different max. In a larger publication by the same authors are reproduced complete absorption curves in neutral, acid and basic media for 169 investigated substances and drugs. A thorough inspection of same reveals that no two compounds give identical curves.

In tabulated form, the extraction and purification process is as follows:

Scheme of Separation

Chloroform Layer equilibrate with 2.5 ml. 0.064-m NaOH. Separate the layers:		Aqueous Layer. Treat with solid $NaHCO_3$ to raise pH to 8 and then equilibrate with 25 ml. Chloroform. Separate layers.	
Chloroform Layer A	Aqueous Layer B	Chloroform Layer C	Aqueous Layer D
Evaporate, dissolve residue in 4 ml. 50% ethanol and determine absorption. Use Table I A	Adjust to pH9 by adding borate solution* and determine absorption. Use Table I B	Equilibrate with 4 ml. 0.1-m H_2SO_4 and determine the absorption of the water layer Use Table I C	Determine the absorption.

*1 ml. 0.10-m H_3BO_3 plus 1 ml. 0.064-m NaOH: pH 9.4.

Deaths from barbiturates, nicotine sulfate, salicylates, strychnine, and quinine lead to drug levels in the blood, that permit identification. To this end, 1 ml. of the blood is subjected to the scheme of separation given below, and this is followed by spectrophotometric investigation of layers A, B, and C. It should be pointed out that this procedure will not permit the differentiation of homologous barbiturates.

For your convenience are listed below some results for compounds isolated in Chloroform Layer A:

TABLE I A

	λ max.	Conc.(ppm.)	% Recovery in layers
Aconitine	228	20	A - 50
Cocaine hydrochloride	232	20	A - 76, C - 4 - 20
Elaterin	234	10	
DDT	236	10	A - 47, B - 5
Opium*	238	25 mg.	
Progesterone	245	10	A - 93
Testosterone	245	10	A - 95
Santonin	245	10	
Rhubarb, USP (sic)	252	25 mg.	
Strychnine Sulfate	255	10	A - 72, B - 2, C - 20
Brucine Sulfate	265	10	A - 48, C - 8
Coffee	272	1 ml.	
Tea	272	1 ml.	
Caffeine (NB)	272	10	A 90
Chocolate (NB)	273	1 ml.	
Coca Cola (NB)	273	1 ml.	
Chloromycetin	278	10	
Cannabis Extract	280	25 mg.	
Cloves	285	25 mg.	
Postum	285-290	25 mg.	
Digitalin	285	100	A - 33
Cubeb	285	25 mg.	
Hydrastine Hydrochloride	295	10	A - 75
Narcotine	312	10	A - 85
Black Pepper	342-46	25 mg.	
White Pepper	342-46	25 mg.	

*Beckman DR

The following compounds distribute themselves in the Aqueous Layer B:

TABLE I B

	max.	Conc. ppm.	% Recovery in layers
Aureomycin Hydro-chloride	220	10	
2,4-D	229	10	B - 82
Tobacco	270	25 mg.	
Coca Extract USP* (sic)	270-74	0.01 ml.	
Tea	272	1 ml.	
Theobromine	273	10	B- 86
Chocolate	273	25 mg.	
Theophylline	274	10	B - 97
Thymol	275	10	
Cinnamon	275-80	25 mg.	
Coffee	280 (see A)	1 ml.	
Marijuana Extract	280	25 mg.	
Coca Cola	283	1 ml.	
6-Chlorothymol	285	10	
Postum	285	1 ml.	
Cloves	342	25 mg.	
Black Pepper	355	25 mg.	
Rhubarb	360	25	
Terramycin Hydro-chloride	370	10	

TABLE I C

In Chloroform Layer C, the following substances were found, measurement in 0.1 m H_2SO_4:

Pilocarpine	215	10	C - 43, A - 37
Rhubarb	224	25 mg.	
Emetine Hydro-chloride	228	10	
Cinchonidine Sulfate	236	10	C - 76, A - 8
Physostigmine	246	10	C - 35, A - 24
dl-Ephedrine Sulfate	257	200	C - 75
Atropine Sulfate· 2 H_2O	257	100	C - 92

*Beckman DR

	λ max.	Conc. ppm.	% Recovery in layers
Homatropine Hydrochloride	257	200	C - 79
Scopolamine	258	40	C - 42, A - 16
Nicotine sulfate	259	11	C - 100
Tobacco	259	25 mg.	
Mescaline Sulfate	268	10	C - 82
Peyote	270	25 mg.	
Apomorphine Hydrochloride	272	2	
Chocolate	273	1 ml.	
Cinnamon	278	25 mg.	
Heroin	279	100	
Curare	280	10	C - 10
Streptomycin	280	1000	
Cloves	280	25 mg.	
Cannabis Extract	280	25 mg.	
Marijuana	282	25 mg.	
Yen Shee*	284	25 mg.	
Cubeb	282	25 mg.	
Nalline	285	100	C - 87
Postum	285	1 ml.	
Coca Cola	285	1 ml.	
Coffee	285	1 ml.	
Opium*	285	25 mg.	

Compounds undergoing ionization and interesting changes in the U.V. spectrum, a) acid solv: 0.1 m H_2SO_4. b) Alk solv: 0.2 m. NaOH:

	a	b
Thymol	274	292
Aconitine	234	226
Cinchonidine sulfate	236	290
Eserine hydrochloride	305	220
Morphine sulfate	285	297
Narcotine	312	281
Nicotine sulfate	259	261
Papaverine hydrochloride	309	238
Quinine	347	232

*Beckman DR

Some entities found in drugs do not exhibit specific absorption in UV light; among the more important ones are: Lactose, picrotoxin sucrose, amylose, citric, fumaric, and succinic acids, pilocarpine arecoline, and digitonin. I would

urge you to retest these values in your laboratories.

Because of its versatility spectrophotometry on a microscale is being used to an increasing extent in official compendia, and it may be only a matter of time until we will routinely use it in pharmacognosy teaching.

In the field of volatile oils, two interesting recent publications deserve attention; they have been used in our college with gratifying results, being accurate and giving reproducible results. Without them we could not have analyzed our small biological samples. The carvone content of Spearmint oil (12) is readily determined in 2 drops of oil: 0.1 ml. is dissolved in 15 ml. methanol and absorption measured at 320 mu. The calibration curve obeys Beer's law.

The USP procedure for menthol determination in Peppermint oil is admittedly difficult to carry out, since its degree reproducibility is low and 5 ml. of oil is required.

Shimizu (13) designed a method where 10 mcg./ml. of menthol or 20 mcg. of oil may be analyzed. The assay involves the reaction with p-dimethylaminobenzaldehyde in sulfuric acid and measurement at 540 mu. This is more specific for the time being than paper partition chromatography (16), since menthone moves along with menthol.

Hardly any alkaloids have been studied as thoroughly as have those from opium. In a recent publication (14), sponsored by the United Nations, an extensive review including 79 references has been made of this field. Since the United Nations does not approve of color reactions in opium since they are not satisfactorily specific, the author suggests a simultaneous study of crystal forms, which is achieved in the following manner:

The test material is dissolved in 1% acetic acid or hydrochloric acid. A microdrop (volume approximately 0.1 λ) of this solution is transferred in a cover slip by means of a glass rod 1 mm. in diameter. A similar drop of reagent is added and the two mixed. The cover slip is inverted and placed on a cavity slide where it rests on thin glass distance pieces cemented on either side to the depression. The hanging drop is now examined under the microscope. As soon as a precipitate can be seen, the cover slip is ringed with 25% gum arabic solution to prevent further evaporation. The drop is examined every few hours and its appearance noted when crystallization

is complete. This may take 24 hours or more. Once a tentative identification has been made, similar crystals should be prepared from a known sample of the alkaloid and compared with those from the test solution. The author tends to insult us by stressing that all glassware used should be well cleaned and thoroughly rinsed, as traces of synthetic detergents may interfere with precipitation.

In its struggle against smuggling and abuse of opium, the United Nations has recently invented methods for the determination of the geographical origin of opium. This is done by flame photometry of the crude opium, and by the composition of trace minerals found therein it can be readily established if the sample is of Chinese, Indian, or Turkish origin, based on the ecological environment of the originating poppy plant.

It is entirely possible that some significant works in this field may have escaped my attention. The problem of omission is greater than lack of material in this rapidly developing science.

As a concluding example of the possibilities in plant extraction and analysis is a method for the isolation of volatile oils. Rovesti (15) extracts the oil with aqueous solutions of surface active materials, breaking the emulsion with salt, and extracting the oil with organic solvent. Several authors have recently found, however, that Clevenger's apparatus still gives the most accurate results.

REFERENCES

1. Vanderwyck, R. W., "A Survey of Pharmacognosy", Am. J. Pharm. Ed., 18, 472-480 (1954).
2. Tunmann, O., and Rosenthaler, L., "Pflanzenmikrochemie", Berlin, Borntrager, 1931.

3a. Ma., T. S., "Organic Microchemistry", Anal. Chem. 30, 760-765, (1958).

b. Maresh, C., et al., "Chemical Microscopy", ibid., 30, 829-838 (1958).

c. Guenther, E., et al., "Essential Oils and Related Products" ibid. 29, 630-37 (1957).

d. Haycock, R. P., et al., "Pharmaceuticals and Related Products", ibid. 29, 697-713 (1957).

e. Bräutigam, F., J. Biol. Phot. Assoc., 23, 105 (1955).

4. Lüdy-Tenger, F., "Der T. B.-Block und einige seiner Anwendungsmöglichkeiten", Pharm. Acta Helv. 22, 460-488 (1947).

5. Rosenthaler, L., and Lüdy, F., "Fällungen von Penicillin mit Basen", ibid 33, 263-268 (1958).
6. Lüdy-Tenger, F., "Mikrochemische Identitätsreaktionen auf Nikotylamid und Nikotinsaure", Mikrochem. 38, 460-465 (1951).
7. Rosenthaler, L., and Lüdy-Tenger, F., "Kaliumfällungsmittel als Alkaloidreagentien", ibid., 32, 35-46 (1957).
8. Sandri, G., Die Bromthalliumsäure als neues Reagens zum Nachweis organischer Basen", Microchim. Acta, 1958, 253-258.
9. Sandri, G., "Über die Verwendung der Goldwasserstoffsäure zum mikrochemischen Nachweis von Alkaloiden und organischer Basen", ibid., 1958, 248-252.
10. Ramstad, E., "Über das Vorkommen und die Verbreitung von Chelidonsäure in einigen Pflanzenfamilien", Pharm. Acta Helv. 28, 45 (1953).
11. Bradford, L. W., and Brackett, J. W., "Systematic Procedure for the Identification of Dangerous Drugs, Poisons and Narcotics by Ultraviolet Spectrophotometry", Microchim, Acta 1958, 353-382.
12. Reitsema, R. H. and Faas, W. E., "Carvone Analysis by Ultraviolet Absorption," J. Am. Pharm. Assoc., Sci. Ed., 46, 381-83 (1957).
13. Shimizu, S., "Studies on Microdetermination of Menthol, Menthone, and Piperitone in the Peppermint Oil by Spectrophotometric and Polarographic Methods", J. Shinshu Univ., No. 4, 292-322 (1954) (In Japanese with English summary).
14. Clarke, E.G.C., and Williams, M., "The Micro-identification of the Opium Alkaloids,", Bull. on Narcotics, 7, No. 3-4, 33-42 (1955).
15. Rovesti, P., Riv. ital. essenze profumi 37, 145 (1955).
16. Hopkins, L. V., and Blake, M. I., "Paper Chromatographic Evaluation of Menthol." J. Am. Pharm. Assoc. Sci. Ed. 48, 222-224 (1959).

RECENT DEVELOPMENTS IN GREENHOUSE AND SMALL GARDEN MANAGEMENT

G. M. Fosler

As a floriculturist, I must admit to having very little knowledge of your particular field. Nevertheless, the new developments and techniques in Horticulture almost certainly would be of interest to you as plantsmen, whether you are concerned with greenhouse or outdoor culture of pharmaceutical plants.

Intermittent Mist Propagation

One of the most interesting and valuable developments in recent years has been the rooting of stem or leaf cuttings under mist. The successful rooting of cuttings has always been an art. But even the highly competent propagator often encounters difficulty using the traditional propagation bench: suitably shaded, regularly watered, high humidity conditions and controlled temperatures. Moreover, quite a number of species could be rooted with little or no success with the old method.

The theory behind intermittent mist propagation is to keep a film of water on the foliage of the cuttings at all times. This practically eliminates wilting, and gives us no particular difficulty with disease organisms. It is then possible to do away with shading. With full sunlight, the cuttings continue their photosynthetic activity and other vital metabolic processes. The net result is often unusually rapid rooting, with few losses. The difficult-to-root items usually respond well too.

There are several precautions to be observed however. Some species, particularly those with hairy leaves, may not stand the high moisture conditions. It is also usually necessary to use a somewhat stronger rooting aid than with the conventional method. For example, if you ordinarily use a No. 2 hormone rooting powder, we recommend that you switch to No. 3 under mist. This is necessitated by the leaching action of the water through the medium.

Another point is that the cuttings, once rooted, should gradually be "hardened off" before removal for transplanting.

Do this by gradually reducing the frequency of misting to zero. It is also essential that the rooting medium be loose, porous, and well-drained. Sharp sand is still as good as anything else we can recommend. Temperature control of the air and medium is still important. To counteract the cooling effect of the water which drains down through the medium, it may be necessary to install heating cables, especially during the cooler months.

Many commercial firms are now in a position to help you set up a mist propagation system. First, consider the water supply. You should have sufficient water pressure to operate the nozzles you have chosen satisfactorily. If not, a booster pump may be needed. And if the water contains much sediment, iron, bacteria, etc., a filtering system should be considered. The two general kinds of nozzles usually employed are the oil-burner and the deflection types. The oil-burner nozzle swirls the water out through a small orifice, resulting in very fine droplets. This type requires somewhat more pressure than the deflection type. The latter has a larger opening and the water is dispersed by deflection against baffles. We find the deflection type most satisfactory where clogging is a problem, and where the water contains a high level of salts which cause the openings to "lime" shut. Our setup uses the so-called "Florida-T" deflection type nozzle.

With the nozzle system installed so that every portion of the propagating bench is uniformly misted, the next problem is to find a device to turn the mist on at intervals. Continuous misting has been tried, but is not advised. Electric timers which automatically open a solenoid valve in the water line are quite satisfactory. During the summer, we find that 4 seconds of misting out of each minute is enough. But this should be adjusted according to the season--and the day-to-day conditions as well. Only enough water need be applied to maintain that continuous water film on the cuttings. Instead of a time clock, you may choose to buy one of the several other devices on the market. These include the so-called electronic "leaf", humidistats, etc.

This is only a brief resume, but I would be happy to supply any of you with references for further reading on the subject, or to direct you to commercial sources of equipment. An excellent new book on plant propagation is "Plant Propagation--Principles & Practices" by Hartmann and Kester (Prentice-Hall, 1959).

Hormone Rooting Substances

The use of rooting aids is well established in horticulture. I have already mentioned that a somewhat stronger formulation is necessary under mist. Rooting powders are used almost exclusively in preference to the liquid forms. The powders are easier to apply (dusted on the cutting bases), and there is less chance of spreading disease organisms than with a liquid into which cuttings are dipped.

A rather new rooting aid called "Chloromone" has recently appeared on the market. And although it is available only in liquid form, we are happy to recommend this product because it has given unusually good results in our propagation tests. A distributor in this area is the Chas. Fiore Nursery, Prairie View, Ill. The manufacturer is the Chloromone Corp. of America, Upper Montclair, N.J.

Water Problems

Water supplies used in growing plants are usually satisfactory in most parts of the country. This is particularly true of water from lakes, reservoirs, and shallow wells which tend to be rather "soft". Deep-well water sources, however, may give rise to problems. In Illinois, for example, water from deep wells often contains a high mineral content--as much as 300 ppm salts. In the home, water softeners can be used to good advantage. But the home-type zeolite softener, charged with NaCl, should never be used with water to be applied to plants.

Repeated applications of this "hard" water to plants, especially in the greenhouse, often causes accumulated soluble salts in the soil. (Water is lost by evaporation, and transpiration from the plant, leaving residual salts in the soil). When the danger level is reached, plants suffer. A side effect comes in the fact that the soil pH may tend to rise well above the level considered best for most plants.

Tests using a Solu-Bridge will quickly tell you whether a high soluble salt condition prevails in your soil. But it is not too simple a matter to remedy the situation. First of all, enough water should always be applied in normal waterings to allow some to drip through the bottom of the pots or greenhouse bench. This will help prevent the salt build-up. For excess levels, heavy leaching is about the only remedy; this may require 4-5 gallons per square foot of soil area.

Incidentally, various nutrients will also be washed out of the soil at the same time. Consult your local extension soil specialist for help in correcting pH levels.

In many areas over the country, water sources also contain high amounts of boron (especially deep-well water). This tends to accumulate in the soil and in plant tissues, and often produces characteristic foliar symptoms. Leaching aids in lowering the boron content of the soil, but will not completely solve this aggravating problem.

Many of you may be concerned about the fluoridation of water supplies, a common practice in many localities. Our tests at the University of Illinois indicate that the amounts of fluorine added (usually less than 1 ppm) have no effect upon plant growth and development. Various test plants required 25 to 50 times that amount to show any deleterious symptoms. Approximately the same thing can be said about chlorine.

Gibberellic Acid

The rather recent "rediscovery" of this material by scientists caused a great flurry among researchers and the general public. Gibberellic acid is a growth-regulating substance which, by now, has been widely tested on various horticultural plants. As far as ornamentals are concerned, rather few practical uses for it have resulted. Geranium blossoms, for example, can be increased in size by spraying the buds with gibberellic acid at the right stage of development. Vegetable specialists apparently find it has some value on leafy vegetable crops. But perhaps the most interesting applications for gibberellic acid are in connection with the breaking of seed dormancy, and in causing certain species to produce seed without special cold treatments or dormancy-breaking treatments.

Problems in Seed Germination

The germination of seeds is still an enigma to many plantsmen. Loss of seedlings due to "damping-off" remains a great problem--although it need not be. Sanitation and proper environmental conditions are "musts". In addition to complete sterilization of the seeding medium, flats, tools, etc., the seed should also be treated with a fungicide such as thiram, captan, or chloranil. Instead of soil, I prefer to use vermiculite for seed germination. The water-retention qualities of this material, along with the fact that it remains well aerated,

makes it an excellent seeding medium. My suggestions: ½-inch of vermiculite over a light soil mixture (2 parts sand, 1 part shredded peat, 1 part loam).

Illinois circulars 793 and 796 give my full recommendations on this subject; write for your free copies. Please note that a temperature range of 65°-75° F. is best for the large majority of seeds with which most of us deal. Again let me emphasize the importance of sanitation. Although many chemical sterilizing materials have reached the market, steam is still the most satisfactory. Aim at 180° F. for 30-45 minutes.

Insect and Disease Control Materials

The rapid development of new insecticides since World War II has made our problem of controlling insects comparatively easy. Among the most useful, both in the greenhouse and out-of-doors, are the organic phosphates: parathion, malathion, TEPP, OMPA, Tedion, etc. Malathion is one of the least toxic of the group to humans and also effective against a wide range of insects. Thus, it currently ranks as one of our "workhorse" insecticides. Beware, however, of using only one insecticide for any length of time; resistant insect strains (e.g., red spider mites) may build up rapidly.

Tedion, perhaps the newest member of the phosphate family, is specific for the control of red spiders (two spotted mites). It is also quite safe to use and has a residual action of 5-6 weeks. Since it is lethal only to the eggs and larval stages, several applications a week apart will be necessary for a complete clean-up. Use 1 lb. of 25% WP Tedion to 100 gallons of water, with a spreader; or, ½ lb. of 50% WP per 100 gallons. It can also be vaporized off of the steam pipes in the greenhouse during the cooler months.

It is interesting to note that antibiotics are gradually becoming a part of our plant disease-control picture. Actidione is now recommended for control of powdery mildew on some plants. Agri-mycin 100 has been found effective against certain bacterial spots, rots, and Botrytis blight.

Among the newer fungicides are Pano-Drench (a mercurial) and Terraclor. Pano-Drench is particularly effective against Rhizoctonia, and is applied as a drench. Terraclor is useful in controlling Rhizoctonia, Sclerotinia, and Botrytis blight infections. Sulfur is still our mainstay for powdery mildew

control, although several other useful new materials for this purpose include Mildex, Karathane, and Omazene.

Weeds under greenhouse benches are notorious breeding places for insects. Use Karmex, Telvar or CMU to kill these weeds. Spray at the rate of 5 tsp. of the 80% W.P. per gallon, to cover 400 sq. ft. Never use 2,4-D formulations in or near the greenhouse.

Evaporative Pad-Cooling of Greenhouses

To overcome excessive greenhouse temperatures in the summer, and to allow us to grow satisfactory crops indoors during this period, several systems of cooling have been tried. Refrigeration cooling is largely out of the picture, and high pressure mist has not proved very satisfactory. At this time, evaporative pad-cooling seems to be preferred. In brief, excelsior pads are installed along one side of the greenhouse. Exhaust fans on the opposite side are used to draw air through the pads and across the greenhouse. Water seeping down through the excelsior pads gives cooling due to evaporation. And the degree of cooling achieved is equal to about 80% of the difference between the outdoor wet-bulb and dry-bulb thermometer readings. Thus, if the outside dry-bulb reading was 100°F., and the wet-bulb reading 80°F., the greenhouse temperature could be effectively reduced to 84°F.

The system is so arranged that a band of cool air exists in the area where plants are growing. The air above and below plant level may be much warmer; all other vents and doors are kept closed. This reduction in temperature is sufficient in most areas to allow excellent crop production (and research) during the hot summer months. As a matter of general information, from 7-10 cubic feet of air must be pulled through the greenhouse per square feet of ground area. And roughly 1 square foot of evaporative pad area is needed for each 150 cubic feet or air moved per minute. No less than 1/3 gallon of water per minute is needed for each linear foot of pad.

Most commercial greenhouse construction firms will be glad to help you plan a custom cooling system of this type. The cost is not excessive. One of the best known manufacturers of pad-cooling equipment is the Acme Engineering & Manufacturing Corp., Muskogee, Okla.

Plastic Greenhouses

The high cost of conventional wooden or aluminum greenhouses often prompts those needing growing space to consider the plastics. Let's look first at the rigid plastics. Certain of these (such as Corrolux or Alsynite) have already been used in greenhouses. These materials are not completely transparent--but are "milky", with embedded fiberglas for strength. Some advantages of this type of plastic over glass include: resistance to breakage and hail damage, diffusion of light, reduced heat loss, and the necessity for only a simple superstructure due to the strength from the plastic's corrugations. But on the debit side are these factors. First, rigid plastic is still expensive. The light reduction may be serious with certain crops, especially in winter. Moisture condensation on the plastic causes aggravating drips. And no one really knows just how long this material will remain usable. Do not attempt to replace glass in a conventional greenhouse with pieces of rigid plastic! **They won't stay in place. Always** choose the nearest-transparent grade offered--never the tinted kinds. At present, the rigid plastics are worth watching, but they are not being widely used for commercial greenhouse construction. The fully transparent plastic known as Plex-o-glass is far too costly to be considered.

Many greenhouses are currently being built using the flexible plastics. Their main attraction is the fact that several of these covering materials are very cheap, and they can be attached to rather simple wooden or metal frames. Polyethylene in the 4-mil thickness can be bought for several cents a square foot. This material, however, lasts only a few months; but its low cost causes it to be widely used for temporary growing structures. Many other plastics, including vinyl, polyester, etc., are being sold for this purpose, most of them also with indifferent success. Perhaps the most promising to date is DuPont's Mylar W. This plastic is now guaranteed for 4 years on roofs and 7 years on greenhouse sidewalls. But it costs about 17-18¢ per sq. ft.

The situation with non-rigid plastics is so fluid that one hesitates to make recommendations. Manufacturers are working overtime to perfect plastics that are better able to weather the elements, particularly ultra-violet rays. Plans for constructing a plastic house are available from many sources. And in many cases these structures provide much needed growing space at a modest cost. However, you should do some careful figuring to determine what the total cost of construction,

maintenance, and regular recovering of a plastic house would be in comparison to a modern aluminum house. The latter should need very little maintenance over a period of many years.

A very recent development, not yet on the market, is a "balloon greenhouse". A shell of clear plastic is kept inflated with a blower-fan, thus eliminating most of the usual supporting members. Obviously there are many problems to be ironed out in this idea, but they may not be unsurmountable.

Sand-and-Peat vs Soil

Why have many florists abandoned soil in favor of sand-peat mixtures for growing plants? First of all, supplies of good soil are hard to obtain in some areas. Furthermore, these mixtures help get around the alkalinity problem, especially in the far west. They also give complete uniformity and are easily and effectively sterilized. Fertility control may be somewhat easier than in some soils. So much interest has been generated in the subject that you may like to get a copy of Manual 23, available for $1.00 from the Agricultural Publications Office, Univ. of Calif., Berkeley. Its title: "The U.C. System of Producing Healthy Container-Grown Plants." In my opinion, the advantages of sand-peat mixtures do not outweigh the disadvantages, at least in many areas. Rutgers scientists are now advocating clay-peat mixtures as a more desirable alternative.

Fertilizers and Soil Testing

The precision growing of crops requires constant attention to nutrient levels in the soil. An experienced grower has the ability to observe plant growth and decide what fertilizing is needed. But this is often a hazardous way of doing it. It's a better plan to submit samples to a reliable soil testing laboratory in your state at regular intervals. Then base your "feeding" program on the results. If you are interested in doing your own soil testing, the Simplex Soil Testing Kit (based on the Spurway Method) is well recommended. It is available from the Edwards Laboratory, Box 318, Norwalk, Ohio.

The use of fully soluble fertilizer materials, rather than mixed dry types, is almost universal in greenhouse establishments. They are easier to apply and are immediately available for use by the plant. On the market today are a number of reliable devices for injection feeding. They allow us to inject a fertilizer stock solution directly into the water

lines. We can then fertilize as we water--a real labor saver. These machines accurately meter the stock solution, regardless of changes in water pressure.

An important new nitrogen fertilizer is known as urea-form--actually a non-soluble plastic made from urea and formaldehyde. It is gradually broken down by bacterial action over a period of months. Thus, it is long-lasting in its effect, yet safe in even excess applications. In general, urea-form (Uramite, Nitroform, Borden's 38) is more useful in outdoor plantings; it is now often incorporated into mixed garden or lawn fertilizers. For general potting mixtures, 3/4 to 1 teaspoonful per 4-inch pot of soil is recommended; in greenhouse benches or outdoor beds, 1 to 2 lbs. per 100 sq. ft. is usually sufficient. Urea-form contains 38% nitrogen.

Iron in the soil is thrown out of solution by pH readings at or above 7. Applications of iron sulfate will only temporarily alleviate this condition. The complex new chemicals known as iron chelates have therefore come into wide use. They not only continue to supply iron under these adverse pH conditions, but also have an acidifying effect. Chelates are said to be faster acting than iron sulfate too.

Fritted potassium, magnesium and certain other elements, are receiving some attention from plant scientists. These essential elements are fused into small glass particles. When mixed with soil, they are slowly released for use by plants. Fritted fertilizers are not generally available, but may eventually find important applications.

Peat Pots

The ordinary clay pot has been with us for a long time--and promises to be around a good while yet. Yet for many purposes, the so-called peat pot has taken over in a big way. It is usually made of a peat-sawdust mixture, vacuum molded into shape, and with fertilizer incorporated. Root development is unusually rapid in peat pots. And this root system tends to be well distributed, rather than matted around the outside of the soil ball as is so often the case in clay or plastic pots.

Plants in peat pots also require considerably less frequent watering. But the biggest advantage lies in the fact that the peat pot is set right into the bench or outside bed with the plant--the roots grow through it. Thus, the root

system is completely undisturbed and plants establish themselves quickly. In addition, the roots are not wounded or dried by being knocked out of clay pots, and there is less opportunity for disease organisms to enter.

Admittedly, peat pots are rather fragile, especially when well moistened. Work is being done to impregnate them with various resins to increase durability. Another approach is to cover the outside with a thin sheath of polyethylene plastic which is pealed off at planting time.

I was recently shown another "container" which is not yet on the market, but which shows some promise. It is merely a compressed block of peat, coated on the outside with a binder to retain its shape. A wetting agent was incorporated in the peat to improve water and liquid fertilizer intake. Young seedlings are merely dibbled into the top of each peat block. In the tests, these seedlings rooted down into the peat rapidly and made excellent growth. When the plants have reached transplanting size, the root systems--peat and all--are set down in the soil. The fact that no soil is required would be a definite advantage. It is always a costly operation to obtain and properly prepare potting soil mixtures.

THE APPLICATION OF FERMENTATION TECHNOLOGY TO PHARMACOGNOSY

D. Perlman

During the past quarter century an increasing number of chemists have been employing microorganisms to carry out desired changes in organic molecules with the objective of producing new substances with useful pharmacological properties. As many of these transformations and syntheses can be accomplished only with considerable difficulty using the standard techniques of organic chemistry, these chemists have learned some of the methods of microbial biochemistry in order to carry out their research programs. Among the purposes of this review are to discuss some of the methodology used by the microbial biochemist, to classify some of the transformations in which microbial processes have been of some use, and to indicate some practical limitations which are often encountered. Some of these topics have been mentioned in recent publications, and reference to these will be helpful for those who plan to use microbial systems as aids in the preparation of new compounds and derivatives. Among these is the review by Eppstein et al. (1) discussing microbial transformation of steroids, the bibliography by Wallen et al. (2) on type reactions in fermentation chemistry, and those papers and reviews dealing with directed biosynthesis including penicillins (3), tetracyclines (4), and cobamides (5).

Inspection of the literature shows that the selection of the microorganism for conversion of a given substrate is usually the factor determining the success of the desired conversion or synthesis. While it is possible to isolate cultures from their natural habitats, e.g. soil, sewage, grains, animal organs, etc., which are capable of carrying out the desired process, for most investigations, microbiologists have relied on microorganisms supplied from public culture collections and repositories. A partial list of the larger collections is given in Table 1. As most of the microorganisms deposited in these collections are classified on the basis of morphological rather than physiological features, it is necessary in repeating observations reported in the literature to make sure that the same strain of microorganism is utilized. It is not unusual to find that different strains of the same species carry out different modifications of the same substrate. For

example, one strain of Fusarium solani converts progesterone to $\Delta^{1,4}$-androstadiene-3, 17-dione (6) while another will not transform this substrate (7). We have also observed that the same strain of Streptomyces fradiae which converts Reichstein's compound S to hydrocortisone in one laboratory (8) converts this compound to epi-hydrocortisone in another laboratory (9). If it is not possible to obtain the special strain of microorganism for the desired transformation, several strains of the species should be tested. Another complimentary problem arises from the proclivity of microorganisms to change their characteristics. We often find that during maintenance of certain strains by standard methods in culture collections that the surviving organisms have lost some or all of their ability to carry out desired conversions or syntheses. Usually an "active" strain can be recovered from a "degenerate" strain by single cell isolation techniques or as a result of mutations. As both of these approaches are rather time consuming, it is sometimes more satisfactory to refer to other sources for the particular strains than to try to "recover" the special strain from an inactive (chemically speaking) culture. The success of a program for producing new drugs which use microorganisms for carrying out certain conversions or syntheses depends upon the reproducibility of the microbial steps, and no effort should be spared in taking care that the microorganisms are maintained in as full vigor as possible.

During the past few years two techniques have been widely used in experiments where conversions of organic compounds were carried out by microorganisms. In the first, the compound to be transformed is added to the growing culture and the growth period is extended until most of the added compound is converted to the desired product. The advantage of this method is in the simplicity of the operation. The cultures of bacteria, molds, streptomyces or yeasts are grown in the normal way, e.g. in either static or aerated culture, and at the end of the incubation period the cells are removed and the product isolated from the fermented medium. As most of the conversions are carried out by adaptive or induced enzymes, the presence during the growth period of the substance to be transformed results in cells containing the desired enzymes. The disadvantages come from the frequent observations that: (1) the added steroid, alkaloid or sugar which is to be transformed is cytotoxic and prevents growth of the microorganism; (2) the growing culture frequently converts the desired product to secondary materials e.g. progesterone is converted stepwise by growing cultures of Streptomyces lavendulae to Δ^{1}-progesterone, Δ^{1}-testosterone, $\Delta^{1,4}$-androstadiene-3,

17-dione and probably to 9, 10-seco-3-hydroxy-1,3,5 (10)-androstatriene-3, 17-dione (10); and (3) the other ingredients of the fermented medium interfere with the chemical isolation of the desired product. In the second method, the microorganisms are grown in suitable media and the cells are separated and resuspended in solutions containing the material to be converted. The conversion period is usually very short and only the desired product is "allowed" to form. Isolation of the desired product from these solutions is usually simpler than from the more complex mixtures found in fermented media. Under certain conditions it is possible to use purified enzymes from the cells rather than the whole cells (11). Equipment and procedures used for growing microorganisms have been rather fully described in the literature (12,13,14).

The successful use of microbial systems rests in part on the availability of sensitive analytical techniques for determining the extent of conversion of substrate to desired product. Filter paper chromatographic methods, filter paper ionophoretic methods, and/or liquid-liquid counter current extraction methods have been very widely used in studying the microbial conversions of steroids (15,16), alkaloids (17), cobamides (18) and antibiotics (19,20,21,22). Some of the analytical methods have also been used as the basis of methods for the isolation and purification of the desired products, while in other instances such sensitive techniques were not required.

Some of the types of transformations of organic compounds by microbial systems are listed in Table 2 together with an example of each. These are only a few of the many examples available from the literature; the bibliography by Wallen et al. (2) lists over 1,300 examples and there have been some 300 more described in the literature during the past six months. Some of the examples of the different transformations of progesterone and related steroids are listed in Table 3. Many research laboratories have been studying microbial metabolism of the steroids, and have shown that many different microbial species carry out the same transformation. Some of the microbial transformations of alkaloids are listed in Table 4. Several of the processes summarized in these tables have been carried out on an industrial scale. These include: (1) oxidation of d-sorbitol to l-sorbose by Acetobacter suboxydans; (2) oxidation of glucose to gluconic acid by Aspergillus niger; (3) condensation of benzaldehyde and acetaldehyde by yeast to form phenyl acetyl carbinol (used in the synthesis of ephedrine); (4) oxidation of hydrocortisone to

prednisolone by Corynebacterium simplex and other bacteria (5) hydrolysis of dioscorea saponins to diosgenin by fungi; (6) oxidation of progesterone to 11-α-hydroxy-progesterone by Rhizopus nigricans; (7) decarboxylation of diaminopimelic acid by Escherichia coli to yield lysine; and (8) separation of the racemic mixtures of amino acid isomers by specific hydrolysis of the N-acetates by fungal enzymes. It seems likely that others of the transformations listed in Tables 2 and 3 will eventually be carried out on a large scale.

In addition to the use of microorganisms to carry out certain conversions of organic molecules, it is possible to use microbial systems in the synthesis of certain types of compounds. For example, certain strains of Penicillium chrysogenum will "accept" precursors and insert them into the penicillins formed by these cultures. It is possible to obtain phenoxy methyl penicillin by adding phenoxy acetic acid to the fermentation, or allylmercapto methyl penicillin by adding allylmercapto acetic acid to the fermentation. Similarly, if Streptomyces aureofaciens is grown in a chloride-free medium, tetracycline is formed, and if the medium contains bromide ions, 7-bromotetracycline is formed (4). If certain chloramphenicol-producing cultures are grown in chloride containing media, chloramphenicol is formed; if the media contains bromide instead of chloride, bromamphenicol is formed, and if no halogen is present the product is N-acetyl-p-nitrophenyl serinol (23). Other examples of directed fermentations are the cobamide-forming fermentations where the organisms normally produce adeninyl cobamides, but will incorporate certain purines, benzimidazoles, phenazines and other molecules into the cobamides instead of the adenine when the fermentations are supplemented with the appropriate precursors (5). While these "directed" fermentations may be of interest to the pharmaceutical chemist, the techniques have not been fully elucidated as yet, and perhaps such syntheses should only be considered when all other methods have failed.

The use of microbial systems to prepare new compounds of pharmacological and pharmaceutical interest is a relatively new idea, and we have not yet reached the stage of technological development when we can consider microbial systems in the same class as chemical reagents. However, with the present rate of progress this day is not far away, and perhaps soon many of the organic chemists will be relying on microbial systems just as they now rely on various chemical catalysts to carry out certain types of reactions. It thus behooves

the organic and pharmaceutical chemist to learn some of the techniques of microbial biochemistry so that he can successfully complete his research programs.

REFERENCES

1. Eppstein, S. H., et al., Vitamins and Hormones 14: 359-432 (1956).
2. Wallen, L. L., et al., Type reactions in Fermentation Chemistry.

   Agricultural Research Service, U. S. Department of Agriculture (ARS-71-13; May 1959).

3. Clarke, H. T., Johnson, J. R., and Robinson, R. The Chemistry of Penicillin. Princeton, N. J.: Princeton University Press (1949).
4. DiMarco, A. Recent Progress in Industrial Microbiology 1: 45-92 (1959).
5. Perlman, D. Adv. in Appl. Microbiol. 87-122 (1959) .
6. Vischer, E., and Wettstein, A. Experientia 9: 371-2 (1953).
7. Perlman, D. (unpublished)
8. Colingsworth, D. R., et al., J. Am. Chem. Soc. 74: 2381-2382 (1952).
9. Fried, J., et al. Recent Progress Hormone Research 11: 149-181 (1955).
10. Peterson, G. E., et al. J. Bact. 74: 684-688 (1957).
11. Levy, H. R., and Talalay, P. J. Am. Chem. Soc. 79: 2658-2659 (1957).
12. Underkofler, L. A., and Hickey, R. J. Industrial Fermentations (2 volumes). New York: Chemical Publishing Co., Inc. (1954).
13. Kroll, C. L., et al., Ind. Eng. Chem. 48: 2190-2193 (1956).
14. Corman, J. et al., Appl. Microbiol. 5: 314-318 (1957).
15. Neher, R. Chromatographic Reviews 1: 140-192 (1959).
16. Reineke, L. M. Anal. Chem. 28: 1853-1858 (1956).
17. Bettschart, A., and Fluck, H. Pharm. Acta Helv. 31: 260-285 (1956).
18. Friedrich, W., and Bernhauer, K. Mikrochim. Acta 134-43 (1956).
19. Jones, T. S. G. Brit. Med. Bull. 10: 224-228 (1954).
20. Block, R. J., Durrum, E. L., and Zweig, G. A Manual for Paper Chromatography and Paper Electrophoresis. New York: Academic Press, Inc. (1958).
21. Snell, N. S., et al. Appl. Microbiol. 4: 13-17 (1956).
22. Ammann, A., and Gottlieb. D. Appl. Microbiol. 3:181-185 (1955).
23. Smith, C. G. J. Bact. 75: 577-583 (1958).

TABLE 1

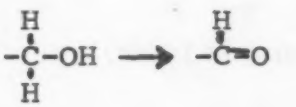
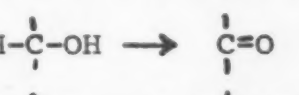
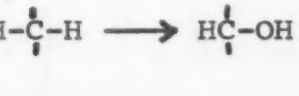
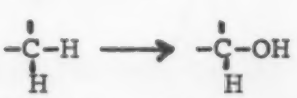
LOCATION OF SOME MICROBIAL CULTURE COLLECTIONS

1. American Type Culture Collection, 2112 M. Street, N.W., Washington 7, D.C.
2. Centraalbureau voor Schimmelcultures, Baarn, Netherlands.
3. Commonwealth Mycological Institute, Kew, Surrey, England.
4. ARS Culture Collection, Northern Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture, Peoria, Illinois.
5. National Collection of Type Cultures, Colindale Avenue, London, NW 9, England.
6. National Collection of Industrial Bacteria, National Chemical Laboratory, Teddington, England.
7. Culture Collection, Research Division, Headquarters Quartermaster Research and Engineering Command, U.S. Army, Natick, Massachusetts.

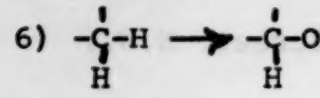
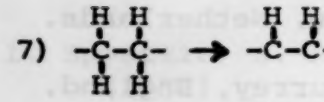
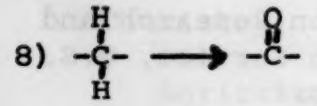
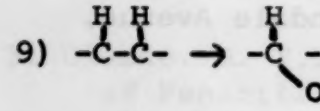
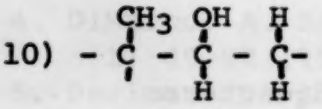
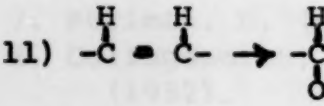
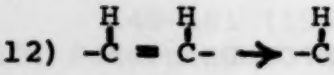
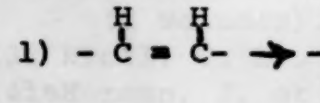
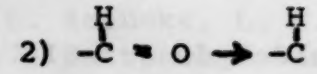
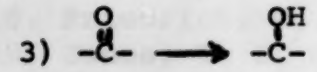
TABLE 2

SOME TYPES OF MODIFICATION OF ORGANIC COMPOUNDS

BY MICROORGANISMS

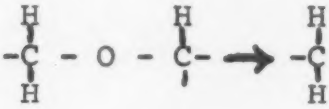
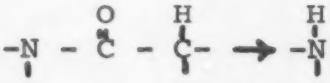
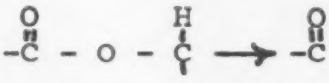
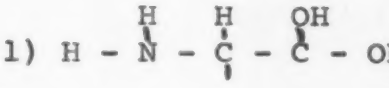
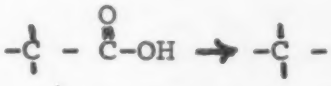
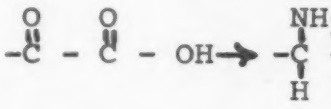
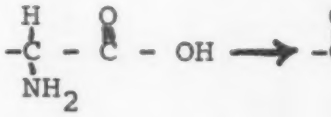
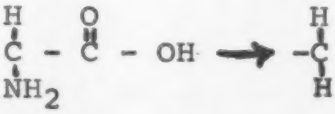
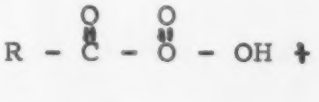
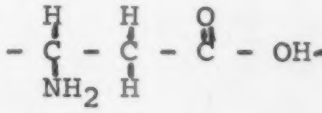
Type of Transformation	Example	Ref.
Oxidations		
1) 	phenethanol to phenacetaldehyde	1
2)	glucose to gluconic acid*	2
3) 	sorbitol to sorbose*	3
4) 	Reichstein's compound S to hydrocortisone*	4
5) 	cortisone to hydrocortisone	5

*Carried out on an Industrial Scale

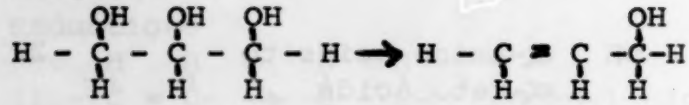
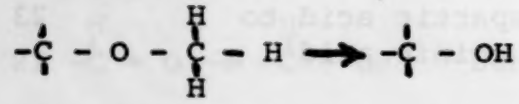
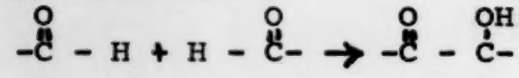
Type of Transformation	Example	Ref.
Oxidations (cont'd)		
6) 	progesterone to deoxycorticosterone	6
7) 	hydrocortisone to prednisolone*	7
8) 	Reichstein's compound S to cortisone	8
9) 	$\Delta^{9(11)}$-Reichstein's compound S to 9α,11β-epoxy-compound S	9
10) 	testosterone to testololactone	10
11) 	hexadecene-1 to (-) 1,2-hexadecenediol	11
12) 	nicotinic acid to 6-hydroxynicotinic acid	12
Reductions		
1) 	cinnamyl alcohol to hydrocinamyl alcohol	13
2) 	benzaldehyde to benzylalcohol	14
3) 	acetol to optically active propylene glycol	15

*Carried out on an Industrial Scale

Type of Transformation

	Example	Ref.
Hydrolysis		
1) 	dioscorea saponin to diosgenin*	16
2) 	penicillin to penicilloic acid*	17
3) 	sterol glucuronide to free sterol	18
Decarboxylations		
1) 	diaminopimelic acid to lysine*	19
2) 	p-aminobenzoic acid to p-aminophenol	20
Amination		
1) 	α-ketoglutaric acid to glutamic acid	21
Deaminations		
1) 	α-amino acids to α-keto acids	22
2) 	aspartic acid to succinic acid	23
3) 2 α-amino acids ⟶ 	glycine plus alanine to pyruvic acid plus propionic acid	24
4) 	aspartic acid to fumaric acid	25

*Carried out on an Industrial Scale

Type of Transformation	Example	Ref.
Phosphorylation		
sugar ⟶ sugar phosphate	adenosine to adenosinetriphosphate	26
Transfer Reactions		
1) transglycosylation	riboflavin to riboflavinglucosides	27
2) transpeptidation	glutamine to glutamylglutamic acid	28
3) transamination	α-ketoglutaric acid plus alanine to glutamic acid plus pyruvic acid	29
4) transphosphorylation	galactosamine plus adenosinetriphosphate to galactosamine-1-phosphate & adenosinediphosphate	30
Racemizations		
1) α-amino acids	lysine*	31
2) α-hydroxy acids	lactic acid*	32
Dehydration		
	glycerol to acrolein	33
Demethylation		
	p-methoxybenzoic acid to p-hydroxybenzoic acid	34
Condensation		
	benzaldehyde - acetaldehyde to phenylacetylcarbinol*	35

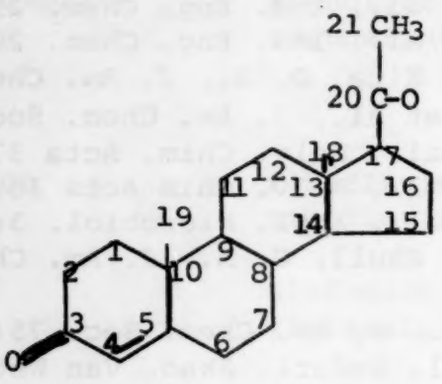
*Carried out on an Industrial Scale

REFERENCES

1. Perlman, D., Abstracts of 119th Meeting, Am. Chem. Soc. April, 1941. p. 24.
2. Moyer, A. J., et al., Ind. Eng. Chem. 29: 777 (1937).
3. Wells, P. A., et al., Ind. Eng. Chem. 29: 1385 (1937).
4. Shull, G. M. and Kita, D. A., J. Am. Chem Soc. 77: 763 (1955).
5. Meister, P. D., et al., J. Am. Chem. Soc. 76: 4050 (1954).
6. Meystre, C., et al., Helv. Chim. Acta 37: 1548 (1954).
7. Vischer, E., et al., Helv. Chim Acta 38: 1502 (1955).
8. Mann, K. G., et al., Appl. Microbiol. 3: 14 (1955).
9. Bloom, B. M. and Shull, G. M., J. Am. Chem. Soc. 77: 5767 (1955).
10. Fried, J., et al., J. Am. Chem. Soc. 75: 5764 (1953).
11. Bruyn, J., Konikl. Nederl. Akad. Van Wetenschappen 57(c): 41 (1954).
12. Harary, I., J. Biol. Chem. 227: 823 (1957).
13. Fischer, F. G. and Wiedemann, O., Ann. 513: 260 (1934).
14. Neuberg, C. and Welde, E., Biochem. Z. 62: 477 (1914).
15. Farber, E. and Nord, F. F., Biochem. Z. 112: 313 (1920).
16. Rothrock, J. W., et al., Arch. Biochem. Biophys. 57: 151 (1955).
17. Abraham, E. P. and Chain, E. B., Nature 146: 837 (1940).
18. Doyle, M. L., et al., J. Biol. Chem. 217: 921 (1955).
19. Casida, L. E., U. S. Patent 2,771,396 (1956).
20. Sloane, N. H., et al., J. Biol. Chem. 193: 453 (1951).
21. Otsuka, S. I., et al., J. Gen. Appl. Microbiol. 3: 35 (1957).
22. Horowitz, N. H., J. Biol. Chem. 154: 1415 (1944).
23. Gale, E. F., Biochem. J. 32: 1583 (1938).
24. Stickland, L. H., Biochem. J. 28: 1746 (1934).
25. Quastel, J. H., and Woolf, B., Biochem. J. 20: 545 (1926).
26. Smythe, C. V. and Robb, L. A., U. S. Patent 2,606,899 (1952).
27. Tachibana, S., et al., Int. Symp. on Enzyme Chem. (Tokyo), paper 116 (1957).
28. Williams, W. J. and Thorne, C. B., J. Biol. Chem. 210: 203 (1954).
29. Meister, A., Adv. in Enzymology 16: 185 (1955).
30. Cardini, C. E., and Leloir, L. F., Arch. Biochem. Biophys. 45: 55 (1953).
31. Huang, H. T., et al., J. Am. Chem. Soc. 80: 1006 (1958).
32. Katagiri, H., and Kitahara, K., Biochem. J. 31: 909 (1937).
33. Smiley, K. and Sobolov, M., Bact. Proc. 14: (1958).
34. Henderson, M.E.K., J. Gen. Microbiol. 16: 686 (1957).
35. Neuberg, C., and Hirsch, J., Biochem. Z. 115: 282 (1921).

TABLE 3

SOME MICROBIAL TRANSFORMATIONS OF STEROIDS



Hydroxylation:	Position	Reference	Position	Reference
	1α	1	11β	9
	2β	2	12β	6
	6β	3	14β	3
	7α	4	15α	4
	7β	5	15β	3
	9α	6	16α	10
	10β	7*	17α	11
	11α	8	19	12
			21	13
*on 19 nor-steroid				
Epoxidation	9β:11β	14	14α:15α	14
Ketone Formation	11	15		
Hydrogenation	20β	16	4,5	10
	20α	17		
Dehydrogenation	1,2	18		
	3α-ol	19	17β-ol	20
Cleavage of side chain		16		

REFERENCES

1. Dodson, R. M., et al. J. Am. Chem. Soc. 79: 3921-3922 (1957).
2. Herzog, H. L., et al. J. Am. Chem. Soc. 79: 3921 (1957).
3. Fried. J., et al. Recent Progr. Hormone Res. 11: 149-181 (1955).
4. Meystre, Ch., et al. Helv. Chim. Acta 38: 381-7 (1955).
5. Murray, H. C. and Peterson, D. H. U. S. Patent 2,602,769 (1952).
6. Schubert, A., et al. Chem. Berichte 2544-2552 (1958).
7. Pederson, R. L., et al. J. Am Chem. Soc. 78: 1512 (1956).
8. Peterson, D. H. and Murray, H. C. J. Am. Chem. Soc. 74: 1871 (1952).
9. Shull, G. M. and Kita, D. A. J. Am. Chem. Soc. 77: 763 (1955).
10. Perlman, D., et al. J. Am. Chem. Soc. 74: 2126 (1952).
11. Meister, P. D., et al. J. Am. Chem. Soc. 76: 4050 (1954).
12. Nishikawa, M. and Haguwara, H. Chem. Pharm. Bull. (Japan) 6: 226-227 (1958).
13. Meystre, Ch., et al. Helv. Chim. Acta 37: 1548-53 (1954).
14. Bloom, B. M. and Shull, G. M. J. Am. Chem. Soc. 77: 5767 (1955).
15. Hanson, F. R., et al. J. Am. Chem. Soc. 75: 5369 (1953).
16. Fried, J. et al. J. Am. Chem. Soc. 75: 5764 (1953).
17. Sweat, M. L., et al. Biochim. Biophys Acta. 28: 391-5 (1958).
18. Nobile, A., et al. J. Am. Chem. Soc. 77: 4184 (1955).
19. Talalay, P. and Wang, V. S. Biochim. Biophys. Acta 18: 300 (1955).
20. Arnaudi, C., Experientia 7: 81-95 (1951).

TABLE 4

SOME MICROBIAL TRANSFORMATIONS OF ALKALOIDS

Substrate	Products	Reference
reserpine	methyl reserpate	1
apoyohimbine	10-hydroxyapoyohimbine and 18-hydroxy apoyohimbine	2
β- yohimbine methyl ether	10-hydroxy-β-yohimbine methyl ether	2
3-epi-apoyohimbine	3-epi-10-hydroxyapoyohimbine	2
yohimbine	10-hydroxyyohimbine	3
yohimbine	18-α-hydroxyyohimbine	4
α-yohimbine	18-α-hydroxy-α-yohimbine	4
nicotine	6-hydroxynicotine and α-(5-N-methyl pyrrolidine) keto acid	5
nicotine	γ-methylaminopropyl-(3-pyridyl)-ketone, (pseudooxynicotine), and 3-succinoylpyridine	6,7
nicotine	6-hydroxy-3-succinoylpyridine	8

(cont'd)

Substrate	Products	Reference
nicotine	ɣ-aminobutyric acid	9
indole	2,2-bis-(3-indolyl)indoxyl	10
indole	tryptophan	11,12
nornicotine	6-hydroxymyosamine	13
anabasine	3-succinoyl-6-hydroxypyridine	13

REFERENCES

1. Glazko, A. J., et al. J. Pharmacol. Exptl. therap. 11: 377-87 (1956).
2. Godtfredsen, O., et al. Experientia 14: 88-9 (1958).
3. Loo, Y. H., and Reidenberg, M. Arch. Biochem. Biophys. 79: 267-80 (1959).
4. Pan, S. C. and Weisenborn, F. L. J. Am. Chem. Soc. 80: 4749 (1958).
5. Frankenbrug, W. G. and Vaitekunas, A. A. Arch. Biochem. Biophys. 58: 509 (1955).
6. Wada, E. and Yamasaki, K. J. Am. Chem. Soc. 76: 155-7 (1954).
7. Wada, E. and Yamasaki, K. Science 117: 152-3 (1953).
8. Hylin, J. W. J. Bact. 76: 36-40 (1958).
9. Casida, L. E. and Rosenfield, R. J. Bact. 75: 474-9 (1958).
10. Loo, Y. H. and Woolf, D. O. Chem. and Ind. 1123 (1957).
11. Malin, B. and Westhead, J. J. Biochem. Microbiol. Tech. Eng. 1: 49-57 (1959).
12. Tyler, V. E. and Schwarting, A. E. J. Am. Pharm Assn. (Sci. Ed. 43: 207-208 (1954).
13. Wada, E. Arch. Biochem. Biophys. 72: 145-8 (1957).

DISCUSSION

Question: Do you use chromatographic methods in the isolation of your compounds?

Perlman: Chromatographic methods have been used in preparations as well as analysis. It is very pleasant to find that you can recover 80% of your transformed product in very pure crystallizable form from a single large paper chromatogram. I think that the methods of paper chromatography and electrophoresis are essential in the work where there are a large number of by-products and you want to be sure that the one you obtain is the one you're interested in.

Schwarting: Are you aware of any system affected by microorganisms involved in the oxidation of methyl groups?

Perlman: Do you mean to methoxyl or carbonyl? I haven't seen this but would not be surprized if such has been reported. Terminal methyl groups of progesterone derivatives are converted to primary alcohols by fungi, and ring methoxyls are oxidized to hydroxyls.

Crane: I've heard that some of the cultures you get from the list on this first page are quite different after they have grown for awhile than they are when they are received.

Perlman: You get a certain amount of adaptation. We have tried to minimize it. You can control it by various methods of stabilizing cultures,e.g., lyophylization of cells. We are gradually changing to washed cell suspensions or dried cells to carry out conversions. We use a definite weight of cells which is added directly to the suspension of chemicals. This cell preparation can be frozen and stored until needed. If your cultures are contaminated, don't try to purify a culture--go back to the original source and let a specialist take the responsibility for identification and purification.

Woodward: Is it known how to proceed from diosgenin to progesterone, commercially--microbial or otherwise?

Perlman: You can use a microbial process--enzymes of Aspergillus, for hydrolyzing off the sugars; most companies are using straight acid hydrolysis. Chemical transformations are used in converting the side chain.

Roscoe: Has anyone tried to get a microbial biosynthesis of a cardiac glycoside?

Perlman: It has been the other way around--a paper will be presented very soon showing a microbial degradation of cardiac glycosides. Several reports in the Japanese literature have described the production or biosynthesis of cardiotonic principles by microorganisms. These have not been identified or clearly elucidated, but there is the possibility of a general relationship.

Dunn: What about the commercial situation here. Is there an arrangement between companies?

Perlman: There generally is a patent or more involved arrangement. Many of the firms buy their synthetic drugs from another; there is constant contact among the commercial operations. As far as laboratory research is concerned, you can get the microorganisms you want to use from whatever their source and usually obtain licenses for processes involving patented organisms.

Youngken: How widespread, besides Streptomyces, are microorganisms that are used for your work?

Perlman: A great many fungi are used and we find the same or similar reactions may occur in many varieties. Transformations are largely carried out by adaptive enzymes formed in a relatively short period of exposure to the substrate.

Schwarting: One of the reactions you don't have on the board, and I'd appreciate the reason why is the synthesis of glycosides. I'd like to hear your opinion as to the formation of a heteroglycoside.

Perlman: Transglycosylation, that is the transfer of sugar residues to alcohols or other sugars, results in the formation of heteroglycosides. Acceptors include riboflavin, ethanol and similar compounds.

CHROMATOGRAPHY AND ELECTROPHORESIS IN PHARMACOGNOSY

Tracey G. Call

The subject, Chromatography and Electrophoresis in Pharmacognosy, is so important that I deem it a rare privilege to be assigned to discuss it before this distinguished group of Pharmacognosists. I am particularly pleased with the assignment because of my personal conviction of the importance of this subject to Pharmacognosists today.

If we are to follow the literature and laboratory work in phytochemistry, it is essential that we understand some of the technics and applications of chromatography and electrophoresis.

As we look to the future, we are also forced to realize that they are important to the undergraduate, as well as to the person engaged in research. A large portion of the abstracts in the biological sciences found in Chemical Abstracts report investigations which have utilized the technics of chromatography or of electrophoresis.

Pharmacognosists abroad, as well as some in the United States, have recently applied these methods in research and occasionally in undergraduate laboratory instruction.

After careful consideration of the method of handling this important topic, I have decided that the most good to the most people will result from a discussion emphasizing the applications, rather than the technics, of chromatography and electrophoresis. Those who have worked in this area are aware of the numerous sources of further information and help. The Crane survey indicates that most instructors do not utilize these methods. It is to those faculty members that this talk is directed. If only a few more people are influenced to try these processes, I shall feel that my report has been worthwhile.

We can briefly classify the methods as follows:

1. Paper electrophoresis.
2. Electrophoresis utilizing other media.
3. Paper chromatography.
4. Column chromatography.
5. Miscellaneous methods such as the chromatostrip, ion exchange, etc.

The method to be used in any individual case will depend to some extent on the type of materials to be isolated, or on the equipment available and the experience of the operator.

Electrophoretic resolution of mixtures is applied more often to proteins, while the chromatographic methods seem to be applied more often to other classes of compounds.

Paper chromatography appears to be the simplest of these methods, and at the same time, it seems to be the most versatile of these methods for the solution of pharmacognostic problems.

In the chromatographic process a mixture is spotted, streaked, or applied near one end of a paper strip, chromatostrip, column, etc. A solvent system is then passed from one end of the medium to the other. The mixture is "strung out" along the path of the solvent as a result of complex interacting partition and adsorptive relationships between the components of the mixture, the solvent system, and the solid matrix.

A similar process is carried out in electrophoresis except that the mixture components are also caused to migrate sideways by an applied direct electric current as the solvent system moves in the other direction.

The equipment needed may be very simple and inexpensive, or it may consist of a complex and costly specialized laboratory.

The result of these processes is essentially that of a separation or isolation of the individual constituents of a mixture.

The relative rate of movement of a component of the mixture as compared with the rate of flow of the solvent system is reduced to a ratio of the distance traversed by the substance as compared to the solvent front. It is expressed in terms of one-hundredths and is known as the Rf (front ratio). The Rf of any substance under similar conditions of solvent system, matrix, and temperature is a fairly constant characteristic of that substance.

The material which has been "spread out" to form a series of spots or streaks on a paper chromatogram can occasionally be observed directly in visible light. The use of ultra violet

light makes other spots or areas visible. Most of the remaining areas covered with separated constituents can be made visible by drying the paper and spraying it with an appropriate chromogenic spray which by color reactions makes these areas visible in ordinary or ultra violet light.

We now have two specific properties of individual substances, i.e., their Rf values and their color reactions. In case we have separated a radioactive material, we may choose to locate it along the solvent path by use of photographic film sensitive to the radiation. The film is simply exposed by placing it on the paper chromatogram.

Two-dimensional paper chromatograms are made by drying a chromatogram and rotating the sheet 90° horizontally and redeveloping it in the other direction with a different solvent system. The original "strung out" series of components is then moved sideways at different relative rates and the components are distributed over various parts of the area of the sheet in a characteristic manner. The relative simplicity of this type of separation and the high degree of purity of some of the separated substances can be particularly satisfying.

Some of the limitations of these methods are the very small yields of isolated material, which in the case of paper chromatography may be in the microgram to milligram range. While this factor limits the utility of paper chromatography for the isolation of active constituents to be tested on animals or for extensive chemical studies, it fortunately does not lessen its value as a guide for other types of isolation procedures. Larger yields can be obtained by column chromatography or by continuous sheet electrophoretic methods.

The utiliaztion of the processes of chromatography and electrophoresis are based on the overlapping divisions of:

A. Qualitative, or detection methods
B. Quantitative, or isolation methods

Some of the applications follow:

Control of Crude Drug Identity and Detection of Contaminants

When a paper chromatogram is made from a very small amount of an extractive from an authenticated crude drug one obtains a specific pattern of spots with certain color

reactions, relative densities and Rf values. An unknown to be tested is used to prepare a similar chromatogram and the densities, Rf values and color reactions are compared. We can often detect differences between species and varieties by the difference in the chromatographic pattern.

In those cases where a difference exists between official species and related species and varieties, we have a good means of detecting substitution or even the addition of small amounts of the other species. The presence of very small amounts of weeds or other foreign organic matter is very easily detected.

The reference chromatographic pattern might be based on the spots produced by the active constituent, or it might be based on nonactive accessory components.

Should it happen in chromatographic processing based on the active constituent, that a related species or variety should yield an identical chromatogram; then that species or variety should in turn be examined to see if perhaps it might deserve official status.

Are our traditional methods able to detect the presence of say two per cent of weeds in a powdered crude vegetable drug? Sectional histology, requiring considerable work, has not been infallible in tests of identity and of quality control.

It seems that it might be advisable at this time to make a thorough study of the possibility of using chromatographic patterns as one of the tests for identity of crude drugs of both plant and animal origin as well as their galenical preparations. I am confident that in a great number of cases they would be specific and definite enough to eventually replace some of the presently used official tests for identity.

In review, we have discussed the application of chromatography to a) tests for identity; and b) detection of adulterants, contaminants, or excess foreign organic matter.

Quantitative Evaluation of Official Crude Drugs and Their Galenical Preparations.

In most cases separation of the active principle of a crude drug must be accomplished before one can determine the quantity of active principle present by means of gravimetric, volumetric, colorimetric or other methods. A large number of

methods of performing this preliminary separation by means of chromatography or by electrophoresis have been proposed. In spite of this, we should be aware of the fact that these methods have been in use for such a short time that they have not yet been tested under many conditions for the separation of natural products.

These methods, in view of their relative simplicity, should be the first thought of chemists and pharmacognosists who are developing isolation or quantitative methods. It is often a relatively simple procedure to quantitatively recover the active principle of a crude drug from a chromatostrip or a paper chromatogram. The eluted material may then be placed in the colorimeter, spectrophotometer, or other instrument for the final step of its quantitative evaluation. In a few cases it is necessary to resort to the use of column chromatography or electrophoresis for the separation.

Phytochemical Investigation

A commonly utilized procedure in phytochemical investigation is to selectively extract the dried plant material with a series of solvents. One begins with the non-polar petroleum ether and progresses through a series of solvents to the alcohols and ends with aqueous solutions of various pHs.

At the time of completion of each extraction step, or even as a test of the completeness of each step, chromatograms may be made in order to determine the nature and quantities of the specific materials extracted by that step.

Frequently the first extraction has been an exhaustive one lasting many hours or even several days. Up to the present time, little utilization has been made of the possibilities of a fractionation within that first step.

A very useful fractionation within this step can often be accomplished by the batchwise addition of small volumes of chilled low boiling point petroleum ether to the prechilled desiccated milled crude drug in an erlenmeyer flask. After shaking for from a few seconds to a minute, the solvent is decanted and the next lot added. Complete removal of volatile and fixed oils and fats is accomplished, with very little removal of most other constituents. Of course, chromatograms are made of each of these petroleum ether extracts in order to decide whether they should be combined or separately processed. This first fractionation within a solvent step often saves

much labor in the processing of the first step of a selective extraction.

After our selective extraction has been completed we may need to further purify one or all of the extracts by means of immiscible solvent extraction systems, either by means of separatory funnels, or by means of a counter current apparatus. What solvent system shall we use? What will be the best volume ratios? The answers to these questions can be answered by means of paper chromatography. This will indicate which way the constituents are going, and in what proportion, at each stage.

The same type of process is applicable to pilot plant runs of commercial extraction and separation procedures. By those means one may select the equipment, methods, and conditions suitable for the most complete and economical operation of the various units. They also help to evaluate the hundreds of fractions one may obtain in some types of column chromatography.

Identification of Compounds

The Rf values determined with several solvent systems and the colors obtained by means of chromogenic sprays are so specific for individual compounds that if we have this data available, preferably filed in a card retrieval system, they may serve to identify compounds with a fair degree of reliability without the necessity of further isolating for other tests. It is, however, usually advisable to make derivatives. These can, however, often be made from the material on the paper. The derivatives are then chromatographed and their properties determined. Hydrolysis and degradation reactions and rates of reaction under various conditions are also easy to follow by means of paper chromatography.

The new Journal of Chromatography is systematically listing the Rf values and color reactions of a large number of compounds. If one is concerned about the destruction of the original invisible material by the use of color reactions, this can be avoided by chromatography of a streak rather than a spot. After development and drying, a strip is cut from the sheet and the areas containing the desired components located by means of the proper reagents. When the strip is fitted back onto the original sheet, the proper areas of the latter can be marked or cut out with confidence in the location of the required areas containing the unaltered substances.

Other Applications

It may be noted at this point that electrophoresis has been used largely for protein separations. Continuous sheet electrophoresis is a practical method for the isolation of larger amounts of material.

A. Partition Coefficients

Chromatography of a series of partition mixtures will reveal in a relatively short time the solubility properties and partition characteristics of a substance.

B. Biosynthetic Processes, Fermentation, etc.

The ease of following the results of biosynthetic processes, fermentation, etc., has led to the rapid determination of optimum temperatures, time intervals, hydrogen ion concentrations, etc., without the necessity of resorting to the laborious conventional analytical procedures.

C. Study of the Results of Ecological Conditions, Growth Effects

The worker in these areas will find numerous applications for chromatography and electrophoresis and thus can more easily determine the effects of his treatments.

D. Genetic Changes and Phylogenetic Relationships

The relationships of chemical constituents to genetic changes and the use of chemataxonomy has been discussed by Dr. Tyler, and about all that might be added at this time is the statement that it seems that chromatography has made possible the completion of many of the investigations to which he referred.

E. Screening Studies

There is a trend in phytochemical studies toward the screening of many natural products in the search for specific compounds or groups of compounds, rather than the examination of single species to find what they contain. It is easy to understand how this trend has greatly increased the efficiency and speed of studies.

F. Pharmacological Applications

Only a few years ago a published study of an investigation by conventional methods reported that flavonoid compounds were not metabolized in the mammalian body. Recently, De Eds and co-workers, utilizing paper chromatography have, in a series of papers (Journal Biol. Chem.) identified a large number of flavonoid metabolites in several animal species and in man. They have worked out the metabolic pathways and by following the degradation of the metabolites have postulated some pharmacological activities which they in turn have been able to confirm.

Studies of metabolic reactions, pathways and the fate of drugs, foods, and body secretions have been rapidly advanced by the utilization of chromatographic methods.

In some cases the diagnoses of various pathological conditions, especially those of endocrine nature, have been made possible by chromatographic means.

The examples I have cited are but a part of the applications of chromatography and electrophoresis to pharmacognosy.

It appears that all pharmacy students who expect to understand research and control procedures or even to understand our pharmacopeias and formularies of the future need to be acquainted with chromatograph technics and applications.

The technics require some practice in order to become proficient, but there are numerous handbooks and descriptions of the methods available. One of the best references is "Partition Chromatography and Its Use in the Plant Sciences", Vol. 25, No. 1 The Botanical Review 1959 (the entire issue) $3.00. This review includes a classified bibliography of 1,466 papers.

Is pharmacognosy the place to teach these methods? I think it is, if the instructor is interested, and learns them well himself. The pharmacognosy of the future will use them. The present is the time to begin the future.

DISCUSSION

Tyler: I'd like to report a device that has cost me much time loss and expense. It is called a centrifugal chromatograph. In my opinion it is of little value.

Call: Thank you, sir, we were interested in it.

Youngken, Jr.: I would like to comment on the Chromatocab with the drawer at the bottom. The drawer offers great difficulty in getting a good seal. Have others had trouble with this seal?

Call: The seal doesn't hold up with continued use.

Martin: Do you have references to volatile oils or fixed oils used for separation by paper chromatography?

Call: Several references are included in my bibliography.

Bulda: I have a device called a Chromatopile which makes it possible to remove a given layer of the chromatogram.

Call: With columns we have gone to continuous separation--these methods are better than what can be done by extruding.

Ramstad: Gas chromatography has been developed recently for separating volatile components. Will you comment on this method?

Call: The U.S.D.A. laboratory at Pasadena is using this method for separation of some mixtures. They consider it very valuable. I have not used it as yet.

Dunn: have you had trouble with fuzzy interfaces of adjacent spots:

Call: That's one of the essential problems of chromatography--a change of the system is necessary to clear this up.

Schwarting: Capillary analysis, the technique of partition chromatography before its modern development, is of interest to pharmacy and pharmacognosy. I would like to relate two events in the early history of the technique that lie in obscurity in usual historical essays on the subject.

F. F. Runge, a pharmacist-chemist, was the first person to explore the phenomenon of capillary migration on paper and other fabrics; the work preceding that of Schoenbein. A rare volume, that I have seen, dates back to 1850 and presents his method and results with inorganic substances and dyes. This apothecary also discovered caffeine.

The second and probably more significant event is that British pharmacognosists practiced a paper partition method for the analysis and characterization of extracts of crude drugs before its modern development. They developed methods which would distinguish closely related pairs of plants (extracts), such as stramonium and belladonna and used the method to detect adulteration.

RECENT ADVANCES IN QUANTITATIVE PHARMACOGNOSY

Marin S. Dunn

A few years ago (1948) Professor J. Hampton Hoch (16) of the School of Pharmacy, Medical College of the State of South Carolina, published an illuminating article on the history of quantitative microscopical pharmacognosy. In this paper, he traced the salient points in the history of this much-neglected and important aspect of pharmacognosy from 1897 to approximately 1945, mentioning the chief contributions over this fifty year span and indicating briefly something of the contributions of each worker. Counting methods, area measurements, work upon palisade ratios, vein islet numbers and stomatal indices were all considered. The reader is referred to this paper as a starting point.

In 1956, Silverman (24) working with the author at the Philadelphia College of Pharmacy and Science presented a thesis entitled "Determination of the Relative Percentages of Selected Members of the Labiatae in Various Broken or Powdered Admixtures". In this paper, he, (Silverman), reviewed the main steps in the history of quantitative pharmacognostical microscopy. He pointed out that the term "quantitative" in pharmacognosy may be used in different ways: (1) to express approximate percentage of the components present in a mixture (2) to include such determinations as palisade ratios, vein islet, stomatal number and stomatal index, etc. (3) to express numerical measurements of various histological elements. Silverman concerned himself mainly with the first and second of these meanings. He carried certain aspects of his literature review up to about 1956.

Looking backward over the period covered by the reviews of Hoch and Silverman, I believe that probably the two most important and exact quantitative methods to evolve were (1) the Lycopodium method of Wallis (32) and his co-workers and (2) the Daisy-Pyrethrum method described by Youngken (39). It is not my intention to review in this paper either of these methods but merely to point out that they have flexibility and accuracy.

The Wallis method can be used with success where characteristic microscopical elements are present in the powder; or where areas of single layered cells can be traced out at known magnification on paper; (such as the epidermal area of

Senna) or where the length of uniformly thick particles can be calculated per unit weight of powder (such as length of rib in Nux Vomica or length of fibers in Cinnamon).

The Daisy-Pyrethrum method which is quite accurate under certain conditions depends for its success upon comparing the average counted number in the unknown powder of some characteristic microscopical element with the number found in the same amount of a known control. The method, modified to suit the material, is capable of application to certain other admixtures and shows some flexibility.

Both the Lycopodium method and the Daisy-Pyrethrum method demand time-consuming weighing determinations.

With this brief review, **and the hope that you,** if interested, will refer to the papers mentioned, I now come to the rather sketchy tracing of the history of certain aspects of quantitative pharmacognosy since about 1945.

For the sake of convenience, I have divided my reference material into the following headings. Certain references belong in more than one category.

A. Some textbooks or reference works having chapters or pages concerning quantitative microscopical methods - published since 1945.
B. Continuation of data-gathering using the older methods and also the examination of factors leading to success or failure of these methods.
C. The establishment of new quantitative yardsticks and/or more radical departures from or modifications of previous methods.

A.

(1) British Pharmacopeia (4) 1958 Appendix XIII Pharmaceutical Press. Under the determination of foreign organic matter, the Lycopodium method is set forth for (a) discrete particles (b) rod-shaped particles and (c) for measurement of area.

(2) Ramstad (21) in his "Modern Pharmacognosy" describes briefly palisade ratio, stomatal index and starch index.

(3) Trease, G. E. (30) a Textbook of Pharmacognosy. 7th Ed. 1957 Chapt. XXXIII Quantitative Microscopy -- pp 773-781.

Contains illustrated discussions of vein islet number, palisade ratio, stomatal number, stomatal index, Lycopodium method and veinlet termination number.

(4) Wallis, T.E. (32) Practical Pharmacognosy 6th Ed. 1953 Part IV - Quantitative Analysis pp 170-186. Although a part of Part IV is devoted to determinations of ash, moisture and volatile oil, still emphasis is also put upon the operation and value of the Lycopodium method. To illustrate - a few of the schedules discussed are given below:-

VIII. To determine the proportions by weight of the constituents of a mixture of powdered drugs.
IX. To determine the epidermal area per grain of powdered Senna leaf.
X. To determine the length of trichome-rib from one milligramme of Nux Vomica.
XI. To determine the length of fibers in Cinnamon bark.
XII. To determine the number of pollen grains in powdered Pyrethrum.
XIV. To determine the number of sclereids per milligramme of olive stones.

The above examples utilize the Lycopodium method, and under each caption, a specific example of the calculation is made.

(5) Youngken, Heber W. (39) Textbook of Pharmacognosy 6th Ed. 1948 Chapt IV. pp 993-1003. Contains a description of the Daisy-Pyrethrum method and its applications, a review of the Wallis Lycopodium method, micrometry, descriptions of vein-islet, palisade ratio, and stomatal index.

B.

Flück and Haller (6) suggested certain modifications of the Lycopodium method such as the percentage of Lycopodium used, the procedure in mixing the Lycopodium and powdered drug and the number of fields to be examined, and in a later article (7), they gave details of the application of their modifications to the determining of the purity of a number of drug powders of the Swiss Pharmacopoeia including Matricaria Chamomilla, Juniperus Sabina, Folium Thymi, Rhizoma Valerianae, Herba Absinthii and Herba Majorana.

In the Quarterly Journal of Pharmacy and Pharmacology, George (9) treated statistically the data obtained in studying

palisade ratios of Atropa Belladonna and A. acuminata.

Rowson (22) studied the significance of the stomatal index for purposes of differentiation in certain species of the genera Atropa, Datura, Digitalis and Phytolacca. He found that the stomatal index proved to be consistent. In earlier work, it was shown the value of the stomatal index was independent of leaf size and habitat of plant and was not very different at different leaf positions. The index of D. inermis suggested it to be a variety of D. Stramonium but D. Tatula seemed to be a distinct species.

Wallis and Santra (33) using the Lycopodium method found the average number of sclereids per mg. of clove stalk to be 1067 and the average area per mg. to be 593 sq. mm. They recommended the use of the area values method for samples of cloves containing quite small amounts of the stalk. They suggested a standard of not more than 58 sclereids per mg. of powdered clove.

Wallis and Santra (34) used the sclereids occurring in large ovoid masses for quantitative determinations in Pimento and found close agreement between calculated numbers and that actually found by their counting method.

The same authors (35) also determined olive stone number in certain powdered vegetable products. Application of this knowledge was useful in determining olive stone amounts in powdered gentian and powdered clove. Maximum error $\pm$ 10%.

Wallis and Santra (36) found from their investigations that the amount of stone cells in commercial black pepper fruits could be determined by the Lycopodium method. The validity of the method was discussed.

The above authors (37) also described methods for determining the percentage proportion by weight of various tissues in white and black pepper friuts.

An interesting and valuable article was published in the Journal of Pharmacy and Pharmacology by Wallis (31) in which he stressed the "concept of mass" in the study of sclerenchyma. The Lycopodium method was the method of choice and the material was stained with phloroglucin and hydrochloric acid. Not only are form and location important, but also information involving number, length, volume and mass must not be neglected.

Boswijk (3) worked upon the value of the stomatal numbers, stomatal indices and palisade ratios of the leaves of one individual of Atropa Belladonna during a season.

Heber Youngken Sr., and William E. Hassan (40) investigated entire plants of A. Belladonna and A. acuminata they raised from authentic seed. They studied among other things, palisade ratio, vein islet number, stomatal number and stomatal index. From their data, they did not find sufficient variation to warrant making a separate species for the Indian variety.

J. L. Forsdike (8) obtained quantitative data such as stomatal index, vein islet number, and palisade ratio for Cassia auriculata, C. acutifolia and C. augustifolia.

Kritikos and Steinegger (17) studying the stomatal index in diploid and tetraploid Lobelia syphilitica showed that the leaves of diploid plants had values varying from 20-22 while in those of tetraploid individuals, the range was from 20.3 - 25.6.

Soos, Kaber and Mandl (29) compared the stomatal indices, vein islet numbers and palisade ratios of nine species of Digitalis.

Hetzer and Volla (15) reported the stomatal counts for the upper and lower surfaces of leaves of 25 representative members of the Compositae - the material obtained from herbarium specimens.

Rudorf and Schwarze (23) found that there are fewer stomata per unit area in tetraploid Datura Tatula plants.

Ballard and Bebarfald (1) in their work on vein islet numbers observed that the use of sodium hypochlorite as a clearing and bleaching agent caused low vein islet counts since the more delicate terminations of the vascular system were destroyed. The best results were obtained using chloral hydrate solution followed by proper treatment with phloroglucin and hydrochloric acid. In small uniform leaves (Buchu, Senna, Coca), the determinations were of value in identification of species but in large leaves, variations due to position, size, environment, etc. reduced the usefulness of the values obtained. In their work, they used a Leitz projector giving 10x-15x magnification and projected the images on appropriately ruled paper. The vein islet numbers were determined for 7 Datura

species and also for Barosma, Cassia, Erythroxylon, and Digitalis. The central part of the lamina gave most uniform results. They found that D. Stramonium and D. Tatula could be differentiated by the vein islet count from each other.

Bedaux (2) found that the determination of the stomatal index and gland index or a combination of both may often be helpful for diagnostic purposes, in the case of Teucrium Chamaedrys. In extreme cases, they were not dependable.

Go and Hegnauer (10) determined the value of the stomatal indices for seven varieties of Datura Stramonium, but did not find them of value in microscopical identification because of inconsistency.

Potůcek (19) applied the stomatal index, palisade ratio and islet count to 15 Mentha species with the object of identification of species and of indication of their systematic relationships but found that due to the great variability of the species, their taxonomic closeness and their ease of crossing, the results were not as satisfactory as hoped.

Hassan and Dunn (13) made a study of the horticultural species of Thymus and published their work in 10 parts. Palisade numbers were determined and stomatal counts made for the different species. In Part II, (14) they determined the palisade numbers of leaves serially located on branches of Thymus Serpyllum and its varieties albus and coccineus. Their study showed that much higher palisade numbers were found in the very young leaves and as leaf area became larger, palisade number decreased. They found that palisade number as a quantitative tool was only valuable in their material from the 4th or 5th pair of leaves or older on the branch. They suggested that very high palisade numbers may furnish one means of separating young from old leaves.

C.

Melville (18) investigated the differential value of starch grain diameter, number of cork cells per unit area and xylem element length in his work on commercial samples of Rio, Minas, Bahia, Manaos, Johote, Cartagena and Nicaragua Ipecacs. As a result, he found starch grain diameter most practical, and he suggested a "9μ starch grain index" (% of grains exceeding 9μ in diameter).

Duquenois (5) pointed out the value of the oxalate index in distinguishing between Cinnamomum zeylanicum (3,300 - 3,800) as compared with that of C. Cassia (50 - 1,300).

Proper and H. W. Youngken Jr. (20) worked out a method for counting the granules in a starch mixture in a saturated zinc sulfate suspension using a Levy counting chamber. The solution had no swelling effect upon the starch and dispersion was efficient. Standard figures for a number of the common starches were obtained and used to estimate their proportions in known mixtures with talc and diatomaceous earth. Chemical estimation showed close agreement.

In their paper of 1951, Hall and Melville (11) introduced and defined the term "veinlet terminations per sq. mm. of leaf surface. Whole leaves of Erythroxylon spp. , Cassia spp. and Barosma spp. were properly cleared and mounted and determinations on whole leaves were made by microprojection thru a 90° prism attached to the ocular onto a calibrated surface placed at a distance of 45 cm. - the apparatus being in a darkened box. Objectives, 16 mm. and 32 mm. and a 6x ocular were used. The paper set forth the details of their method. A number of positions from base to apex of the leaf were examined for 20 leaves of each species and the veinlet terminations and vein islets counted per sq. mm. A table of variance is given since the data is treated statistically. The authors found (1) no significant correlation between veinlet termination number and the number of vein islet per sq. mm. (2) veinlet termination number was independent of the area of the leaf and was not significantly dependent on position of leaf where determined (3) veinlet termination number may be used to differentiate coarse powders of certain leaves.

In a later paper, the same authors (12) extended their work, using whole leaves and coarse powders of Atropa Belladonna L. and Digitalis purpurea L. The data was again treated statistically. The means for veinlet termination number obtained on coarse powders did not deviate much from those obtained on whole leaves. The paper reported data obtained from the study of coarse powders of a number of other genera and species (Atropa acuminata, Royle ex Lindley, Hyoscyamus niger L. and Datura Stramonium and those species used in the previous paper).

The authors reported that leaves either whole or in coarse powders of all the co-generic species examined could be differentiated by their veinlet termination number with the

exception of B. betulina and B. crenulata. A list of the advantages of the use of veinlet termination number method was given, - the lack of the need for special equipment, the ease of counting, etc.

Wellendorf (38) counted the number of idioblasts containing "sandy crystals" per sq. mm. in distinguishing Belladonna leaf adulterated with Scopolia carniolica. For Scopolia, the value varied from 5 - 8; for Belladonna, about 20. It was suggested that if the value was below 10, a palisade ratio count should be made for confirmation.

Silverman and Dunn (25) introduced the term "palisade number" in their work on the separation, microscopically, of peppermint and spearmint, either as whole leaves or in the powdered condition. The material properly cleared and mounted was examined, using the 43x objective and 10x ocular with a Howard Micrometer Disc in place on the ocular diaphragm. The area counted was that of one of the small centrally-located squares of the Howard ruling, and the object counted was the upper ends of the palisade cells. The palisade number of Mentha spicata L. had a range of 12-33 and an average of 20, while that of Mentha piperita L. ranged from 5-13 with an average of 9.

In a later paper (26) the same authors, applied the general principles of their method to the approximate quantitative determination of admixed peppermint and spearmint. Directions were given in the paper for clearing, staining and mounting in the Levy Leucocyte counter (Fuchs-Rosenthal double ruling). Then with the ocular net in place, the epidermis-palisade particles were identified and counted. The particles in 8 separate leucocytometer chambers were thus identified and counted. To determine the approximate percentage of each, in the mixture, each drug's unit total was divided by the combined total and multiplied by 100. A table was presented showing the actual and calculated percentages and the percentages of variation in seven samples.

In a still later paper (29), the same general method was applied to admixtures 2 to 5 component drugs (spearmint, peppermint, thyme, sage, rosemary, marjoram). The results were given in table form. In the cases of thyme, sage, rosemary and marjoram, the count was based on a microscopical characteristic diagnostic of the presence of each and not of the others. These characteristics (for each) were described and illustrated in the paper.

One of the advantages of the method used was the elimination of very accurate, time-consuming weighing operations.

In a fourth paper (28) there was presented a statistical analysis and discussion of the data obtained in separating spearmint and peppermint.

SUMMARY

The paucity of references in the account just given is due in part to the lack of workers in this most interesting and rewarding field of quantitative microscopy. Those who engage in this type of research are intelligent and devoted to their work, and it is due to zealous investigators like Meyer, Kramer, Wallis and Youngken, to mention only a few, that the science of quantitative pharmacognosy has made the strides it has. The work is not spectacular; it is often hard and long and tedious; there is very little applause for the job satisfactorily completed. And the reward is often only the inner glow of satisfaction that comes from a job well done. For anyone whose interests lie along the lines of microscopy, quantitative microscopy offers great possibility and opportunity.

TENDENCIES

in Quantitative Microscopy as applied to Pharmacognosy as seen during the last 15 years:

(1) Wallis and his co-workers have been perfecting the Lycopodium method showing its accuracy and flexibility.
(2) More emphasis has been placed on the use of statistical evaluations as a necessary tool.
(3) Much data has been collected showing the advantages and disadvantages of the palisade ratio, stomatal number, stomatal index and vein islet count. And, in some cases, those values have been found useful for diagnosis.
(4) A few new yardsticks (palisade number, veinlet termination, starch index) have been employed.
(5) An attempt has been made to develop a rather rapid method for approximate quantitative analysis of mixed powders of certain vegetable drugs.

But the whole picture points up the need for interested, intelligent, trained, careful workers to develop new techniques and methods and to improve on old ones in this most interesting field of Pharmacognosy.

BIBLIOGRAPHY

1. Ballard, C. W. and R. Bebarfald, Validity of vein islet numbers in species distinction. Jour. Amer. Pharm. Assoc Sci. Ed. XLII: 13-16. 1953.
2. Bedaux, F. C., Een experimenteel onderzock betreffende de stomata-index en klierhaar index, van Teucrium Chamaedrys (An experimental investigation of the stomatal index and gland index of Teucrium Chamaedrys) Pharmaceut. Weekblad 89 (51/52): 889-897. 1954. (Bio. Abstr. Vol. 29: p 2937, #29518)
3. Boswijk, D. G., Quantitative microscopical measurements, Pharm. Weekbl. 83:225. 1948 (Abstr. Quart. Jour Pharm. and Pharmacol. XXI: 534. 1948).
4. British Pharmacopoeia., Appendix XIII: p 892, Pharmaceutical Press, London. 1958.
5. Duquenois, P., Contribution a la normalisation des drogues vegetalis. I. signification et valeur de quelques indices chimiques (Contribution to the standardization of vegetable drugs I. significance and value of some chemical indices) Ann. Pharm. Francaises 5(3): 155-159, 1947. (Bio. Abstr. vol. 22: p 1939 #19231).
6. Flück, H. and V. Haller, Quantitative microscopy of powdered drugs., Pharm. Acta Helvet. 20:92, 1945. (Abstr. Quart. Journ. Pharm. and Pharmacol. XIX: 77. 1946).
7. Flück, H. and V. Haller, Quantitative microscopy of powdered drugs.II., Pharm. Acta. Helvet. 20:509, 1945. (Abstr. Quart. Journ. Pharm. and Pharmacol. XIX: 77. 1946).
8. Forsdike, J. L., Palthé Senna as an adulterant of Indian Senna. Journ. Pharm. and Pharmacol. 1:34-37. 1949.
9. George, E., Palisade ratio values of Atropa Belladonna and Atropa acuminata, Quart. Journ. Pharm. and Pharmacol. XIX: 144-154. 1946.
10. Go, Liem S. and R. Hegnauer. (V.Leyden), Pharmacognostische onder-zoekingen mit Zeven vormen van Datura Stramonium (Pharmacognosy of seven varieties of D. Stramonium) Pharmaceut. Weekblad. 90 (15): 513-519. 1955. (Bio. Abstr. vol. 30: p 1727 #17558).
11. Hall,J. P. and C. Melville, Veinlet termination number. A new character for the differentiation of leaves. Journ. Pharm. and Pharmacol. 3: 934. 1951.
12. Hall,J. P.,and C. Melville, Veinlet termination number. Some further observations., Journ. Pharm. and Pharmacol.6: 129-133. 1954.
13. Hassan, I. and M. S. Dunn, Studies of the genus Thymus. (in ten parts). Amer. Jour. Pharm. 1957, 1958.

14. Hassan, I. and M. S. Dunn, Studies of the genus Thymus. The palisade numbers of leaves serially located on branches of Thymus Serpyllum particularly its varieties albus and coccineus. Amer. Jour. Pharm. 130: 43-51. 1958.
15. Hetzer. W. A. and L. D. Volle, stomatal counts of Kansas species in certain genera of the Compositae, Trans. Kansas Acad. Sci. 53 (3). 1950. (Bio. Abstr. vol. 25 p 2230 #24873).
16. Hoch, J. H., Fifty years of quantitative microscopy in Pharmacognosy. Economic Botany 2:111-116. 1948.
17. Kritikos, P. G. and E. Steinegger., Heteroploidie - Versuche an arzneipflanzen 8. Spaltöffnungs-index bei diploiden und tetraploiden Lobelia syphilitica (Heteroploidy research on medicinal plants 8. The stomatal index in diploid and tetraploid L. syphilitica). Pharmaceut. Acta Helvet. 24 (2): 45-50. 1949. (Bio. Abstr. vol. 24 p 1356 #14067).
18. Melville, C., Ipecacuanha-differential histological characters for the commercial varieties. Quart. Jour. Pharm. and Pharmacol. XIX: 292-301. 1946.
19. Potůcek, O., Beitrag zur mikroskopichen bestimmung der blattdrogen der gattung Mentha L. (contributions to the micro-determination of leaf drugs from the genus Mentha L.) Pharmazie 11 (7): 478-485. 1956. (Bio. Abstr. vol. 32: p 1167 #13837).
20. Proper, R. L. and H. W. Youngken, Jr., A quantitative microscopic study of certain commercial and vegetable drug starches. J. Amer. Pharm Assoc. Sci. Ed. XXXVII:166-172. 1948.
21. Ramstad, Egil., Modern Pharmacognosy p 434. McGraw Hill Book Company Inc. N. Y. 1959.
22. Rowson, J. M., The significance of stomatal index as a differential character. Part III. Studies in the genera Atropa, Datura, Digitalis, Phytolacca and in polyploid leaves. Quart. Jour. Pharm. and Pharmacol. XIX:136-143 1946.
23. Rudorf, W. and P. Schwarze. Polyploidie - Effekte bei Datura tatula. Planta 39 (1):36-64. 1951. (Bio. Abstr. vol. 25 p. 3138 #35566).
24. Silverman, H. I., The determination of the relative percentages of selected members of the Labiatae in various broken or powdered admixtures. (A thesis presented to the faculty of the Philadelphia College of Pharmacy and Science as partial fulfillment of the requirements for the degree of doctor of science in pharmacy) May 1956.
25. Silverman, H. I. and M. S. Dunn, comparative palisade numbers as a means of microscopically identifying and separating peppermint and spearmint leaves. Amer. Jour. Pharm. 128:19-23. 1956.

26. Silverman, H. I. and M. S. Dunn, The application of the palisade number method to the quantitative determination of spearmint and peppermint when in powdered admixture. Amer. Jour. Pharm. 128:98-102. 1956.
27. Silverman, H. I. and M. S. Dunn, The determination of the relative percentages of selected members of the Labiatae in various powdered admixtures. Amer. Jour. Pharm. 128: 225-234. 1956.
28. Silverman, H. I., Dunn, M. S. and J. L. Ciminera, A statistical study of the palisade numbers of peppermint and spearmint leaves. Amer. Jour. Pharm. 129:205-210. 1957.
29. Soos, E., Kaber, I.and A. Mandl., Microscopical characterisation of Digitalis species. Sci. Pharm. 18:135. 1950 (Abstr. Jour. Pharm. and Pharmacol. 3:443. 1951.
30. Trease, G. E., A textbook of Pharmacognosy. 7th Ed. Chapt. XXXIII. pp 773-781 Williams and Wilkins Company, Baltimore 1957.
31. Wallis, T. E., Sclerenchyma in the diagnosis and analysis of vegetable powders. Jour. Pharm. and Pharmacol. 1:505-513. 1949.
32. Wallis, T. E., Practical Pharmacognosy 6th ed. pp 178-186 J. and A. Churchill Ltd. London. 1953.
33. Wallis, T. E. and D. K. Santra., Determination of clove stalk in powdered clove. Quart. Jour. Pharm. and Pharmacol. XX:291-299. 1947.
34. Wallis, T. E. and D. K. Santra., Pimento: a numerical study of its sclereids. Quart. Jour. Pharm. and Pharmacol. XXI: 38-44. 1948.
35. Wallis, T. E. and D. K. Santra., Determination of olive stones in powdered vegetable products. Quart. Jour. Pharm. and Pharmacol. XXI:312-320. 1948.
36. Wallis, T. E. and D. K. Santra., Pepper and pepper-husk. Jour. Roy. Microsc. Soc. 69 (345):9-17. 1949. (Bio. Abstr. vol. 23: p 3107 #30135).
37. Wallis, T. E. and D. K. Santra., Pepper and white pepper shell. Jour. Roy. Microsc. Soc. 69(346):76-85. 1949. (Bio. Abstr. vol. 24: p 1294 #13394).
38. Wellendorf, M., Adulteration of Atropa Belladonna. Dansk Tidsskr. Farm. 30:281. 1956. (Abstr. Jour. Pharm. and Pharmacol. 9:563. 1957).
39. Youngken, H. W., A Textbook of Pharmacognosy. 6th ed. Chapt. IV. pp 993-1003. The Blakiston Company, Philadelphia. 1948.
40. Youngken, H. W. and W. E. Hassan, Jr., Pharmacognostical and chemical studies of Indian belladonna. Jour. Amer. Pharm. Assoc. Sci. Ed. 37:450-458. 1948.

DISCUSSION

Call: What is the distance between two lines on your stage?

Dunn: It will depend on the magnification system. But really, in these measurements the distances aren't so important so long as all items are measured by the same units under the same magnification.

Crane: What was your conclusion about the origin of trichomes appearing to arise from 2-3 adjacent cells on the leaf of Thyme reported by Hassan at Montreal? I still can't believe they arise as he reported them.

Dunn: Hassan didn't finish that investigation. He published the paper and went directly to his home. I find it hard to believe that they arose that way also.

Youngken Jr.: Might not a multiseriate trichome arise from adjacent cells?

Dunn: We have no examples on hand of this sort of thing. It is possible that a multicellular trichome might arise this way.

Ramstad: The normal pattern of division is at right angles to the epidermis which would result in a single row of cells of a trichome.

Youngken Sr.: It is possible for a uniseriate trichome to arise from two adjacent cells.

Dunn: I intend to get an answer to this eventually.

MICROSCOPY OF DIGESTED FOODS

A POSSIBLE CONTRIBUTION TO FORENSIC SCIENCE

Paul D. Carpenter

About 10 or 12 years ago, the state toxicologist, Dr. Walter J. R. Camp, who is also Professor of Pharmacology in the Department of Pharmacology in the Medical School, asked me to look at some food material from a stomach that was sent to him for toxicologic examination. He explained to me that food found in the stomachs of murder victims or individuals where the cause of death is unknown or uncertain has long been used as a means, primarily, to (1) aid in establishing the time of death or (2) to perhaps trace the whereabouts of the person prior to death. Dr. Camp, who is a toxicologist of international reputation is quite able to identify most foods in the stomach, macroscopically, especially if digestion (both chemical and mechanical) has not proceeded too far. Microanalysis of food, however, is outside of his vast field of knowledge. So, I became a consultant to him when macroscopic analysis was not revealing or was uncertain - which is often the case when digestion has gone on for a considerable length of time or when the food particles are of a less common food. At the level of the stomach, most ingested foods can be identified by characteristic histologic elements or structures, even such foods as mashed potatoes, in which there is little other than thin-walled parenchyma and partially digested, hydrolyzed and much distorted starch grains (distorted from cooking). Food remains in the stomach some four hours. Thus, the state of digestion gives a rough estimate of the time elapsed since ingestion and if someone has information about the victim's last meal, the time of death, within limits, might be established.

Examination of vomitus has been of value in some investigations. The only experience I have had with this, however, was in a case where vomitus was found on the clothing and in the car of a suspect in the murder of a girl on the south side of this city. Microscopic examination of the vomitus and remaining food in the victim's stomach were composed of the same food elements. This fact, I was told later was a most damaging piece of evidence to the suspect and was largely responsible for an early confession of the crime committed by him.

Several years ago the feces of an infant was sent over to our laboratory by a parasitologist in the medical college. She wondered if the many segmented structures, worm-like in appearance, present in the feces could be of vegetable origin since they could not be identified as an animal parasite. It was indeed of plant origin. The worm-like segments were identified as chains of oleo-resin cells from banana, part of the infant's diet.

It occured to me that the microscopic examination of feces or of intestinal contents at various levels of the digestive tract for food elements might be of some value (comparable to the examination of stomach contents) in forensic investigations. It might be of considerable value in cases where the stomach was completely empty.

With this in mind, I undertook the microscopic examination of feces after ingestion of various foods to determine if enough material would traverse the entire digestive tract to make identification of most ingested foods possible.

After ingestion of the foods commonly used and some less common foods, microscopic examination of fecal material showed that practically all foods of vegetable origin particularly, could be identified by various tissues, cells and histologic structures present in the feces. Foods such as mashed or boiled potatoes or peeled fruit where there is little or no lignified or cutinized tissue and are composed almost entirely of thin-walled parenchyma are difficult or impossible to identify. The parenchyma cells can be seen but they are collapsed, distorted and without contents. They appear very similar, for example in the foods just mentioned.

There is no appreciable change in most cells with thick walls of cellulose or fragments of tissues containing lignin, resins, oleoresins, tannins, or cutin. Actually, small fragments of tissue resulting from the mechanical break down and from the digestive processes are in an ideal physical condition for microscopic examination -- frequently in groups of only a few cells. Furthermore, most tissue is nicely stained a yellow to dark brown from the relatively long contact with the bile pigments.

Incidentally, certain food elements are identifiable macroscopically, such as raspberry seed, tomato seeds, larger pieces of nut meats and fruit skins in general.

In cooperation with Dr. Camp, practical application of this kind of microanalysis has been made in several crime investigations with significant results. I will briefly outline one of these cases, which occured here in Chicago, not too long ago.

On the night of December 28, 1957, two teen-age sisters failed to return home after attending a movie. On January 22, 1958, some four weeks later, their nude bodies were found in a ditch along a roadside. During this period no one reported seeing them. The temperatures ranged from -13 to 28 above zero with considerable snow throughout this time, until a day or two before they were found, when the temperature went to about 58 degrees.

After the bodies were found, much publicity resulted and the girls' pictures appeared in the newspapers. Several people reported having seen the girls alive, at various times and locations during the month they were missing. One woman said she saw the girls in a restaurant with a character from skid row three weeks prior to the date on which they were found. She identified a young man to the authorities as the one she had seen with them.

This man confessed to the crime. He made several conflicting statements of his acquaintance and behavior with the two girls. Briefly, the main points of his confession were these: He met the girls on January 7th (where were the girls from December 28th to January 7th?). He told of episodes of drinking, immoral sexual behavior and general debauchery, for a period of a week or until January 13th. He said another man, he described as a buddy, had joined them.

On the night of January 13th, according to the confession, the foursome, were on a beer drinking tour of taverns and finally visited a restaurant where they consumed several hot dog sandwiches. A little later they drove to a seldom traveled road in a country area where the girls were beaten to unconciousness, disrobed and tossed out of the car into the ditch beside the road.

Many of the so-called "facts" of the confession could not be confirmed by the findings of the pathologists. For example, the bodies were free from any marks of violence. There was no evidence of any sexual violence having been committed. Dr. Camp's toxicologic examination of the internal organs showed nothing of a toxic nature and no trace of alcohol.

Furthermore, there was disagreement among the pathologists and other investigators as to time of death. The bodies were both in an excellent state of preservation and some believed the girls had not been dead for long, 2 or 3 days perhaps, 9 days according to the confession.

We hoped an examination of the intestinal contents might be of significance and possibly give some evidence regarding the time of death.

Dr. Camp found a small amount of stomach contents in one girl, but none in the other. He gave this and the contents of the lower digestive tract (colon, rectum) of both girls, plus a small piece of feces found with the bodies, to me for microscopic examination.

The small amount of material -- found in the stomach of the one girl -- none in the other -- consisted of about one ounce of a brownish liquid with a few fragments of peanuts and a bit of fibrous material which was identified as tracheal tissue from sweet potato (yam). No hot dog or meat of any kind was found in the stomach. We recognized, at once, that the confession of the suspect was faulty regarding the ingestion of hot dog a short time prior to death.

Investigation of fecal material in both girls revealed much. Both had fragments of wheat (not from white bread, but from some form of wheat breakfast food or perhaps whole wheat bread). The slide shows large pieces of epidermis with several trichomes. In white bread, only a few single trichomes are found.

In the eliminated feces (undoubtedly the oldest material examined), two or three fragments of sage leaf were found.

In both girls quite a large number of rosettes of stone cells from pear were found.

There were also fragments of epidermal tissue from pea, and a few fragments of apple skin found in both girls.

In both girls, in the upper regions of the sigmoid colon, were found many fragments of tracheal tissue from yam. Bits of peanuts and peanut skin (testa) were numerous in this region. Also found were muscle fibers of fish. This identification was possible after careful measurements of the striations of known fish muscle fiber (tuna and sardine) and of fibers from

mammalian meat (pork and beef) were made. The striations of skeletal muscle from fish are much finer and closer together than those of mammalian skeletal muscle fibers.

A few seeds of raspberry and what I believed were a few styles and stigmas from the same fruit were found in the colon of the younger of the girls along with some oleoresin cells from banana.

Subsequently, the investigators of the crime who had no knowledge of the results of the microanalysis obtained the following information:

1. An interview with the girls' mother was held, regarding any knowledge she might have of the food the girls may have eaten on the 26th, 27th or 28th of December. The mother stated that on December 26th, she knew definitely that both girls ate leftover dressing, turkey and gravy. The dressing was made with bread, onions, potatoes, sage and salt and pepper. She further stated that all of her children were in the habit of eating dry cereal for breakfast and that she kept an assortment of cereal in the pantry.

On December 27th, the mother stated she could not recall what she had prepared for the family dinner and did not know what the girls may have eaten for breakfast or lunch.

For the evening meal, on December 28th, both girls ate white and sweet potatoes mashed together, tuna fish and mayonnaise on white toast, chocolate chip cookies and pepsi-cola. She stated that the girls ate out on Fridays and that one always ordered toasted cheese sandwiches and french fries. She also said, that on all of these days there were apples, oranges, grapes and assorted chocolates in the house, which the girls may have eaten.

2. A brother of the girls said he had treated his younger sister to a banana split in the early afternoon of December 28th.

3. A friend of the girls stated that she saw both girls eating candy bars and popcorn at the show that night.

The findings of the tracheal tubes from yam in the upper regions of the colon of both girls (and even a small fragment still in the stomach of one) and of fish muscle fibers corresponded with what the mother had prepared for their supper the night of their disappearance.

The findings of banana oleo-resin cells and raspberry seed in the colon of the younger girl correlated with the banana split her brother had bought for her.

The presence of pieces of peanut and fragments of the seed coat of peanut could be from the candy bars they were seen eating at the theatre. Popcorn was subsequently found. The pears and peas could have been consumed on December 27th, the day no one had knowledge of the food eaten by the girls. The few fragments of sage leaf in the oldest fecal material examined could be accounted for by the ingestion of leftover dressing on Dec. 26th.

All this evidence substantially established the fact that the girls had died some time during the night of Dec. 28th or early morning of Dec. 29th. It would be highly improbable and fantastic to believe that the girls could have lived days or weeks and then consumed, at a later date, prior to death this same combination of foods and in the same sequence.

With these findings added to those of the pathologist (no evidence of physical violence and no sexual assault), the suspect's confession was totally discredited and he was released by the state's attorney. The mother was considerably relieved for it sustained her belief that her girls would not have deliberately left home and behaved as the suspect had described. The crime is still unsolved.

Examination of fecal material from a person who has died under suspicious circumstances and where the time of death is questionable, greatly extends the period over which the time of death might be determined if something is known of the food ingested prior to death. (This is limited to about four hours by stomach content examination). It may extend the time to 30 or more hours - perhaps as much as 3 days. At various levels of the colon where the feces lose much water and is not mixed with previous or later additions of material it is possible to find fairly well delineated sections which contain fragments from food ingested at breakfast, lunch and dinner or even foods ingested longer ago than this, depending upon the time of the last defecation. There is a built-in time clock, particularly in the sigmoid colon, rectum, or in eliminated fecal matter.

I will not go into details of preparing the slides because of the limited time here, other than to say, a small bit of material is obtained at various levels of the digestive tract

or from eliminated feces - dehydrated with alcohol, and cleared with xylol. The xylol has an asthetic value also. It is examined in xylol or made into permanent mounts in Canada Balsam. If any of you are interested in further details, I shall be glad to talk with you about it in the laboratory and show you some of the original slides.

Pathologists, at autopsy, must appreciate the significance of this technique and should carefully preserve specimens of intestinal contents when present at several different levels of the digestive tract and submit them to qualified persons for analysis. My experience with personnel in crime detection laboratories has convinced me that, although they are, indeed, well-qualified and clever in microanalysis of many items, such as dirt or soil, fibers from clothing, hairs, chips of paint and many other substances that are of great value in the total investigation of many crimes, not many are familiar with the plant tissues so characteristic of the different foods used by man. Pharmacognosists are microanalysts of plant tissue!

I think it would be of great benefit to you and to society, if you would contact the crime laboratories in your city or near-by cities where such laboratories exist and let them know of your special knowledge and ability to analyze and identify materials of vegetable origin.

I have shown how microscopic examination of fecal material has been practically applied in forensic investigation. However, I believe more research is needed- and this suggests some studies for graduate work. Studies should be made to determine more accurately, if possible, the time element in the processes of digestion and elimination. What range of variability is there in different individuals? male? female? in physical (or mental) condition of the subject (pathology)? Is age a factor? What is the time variation in the passage of different types of foods through the entire digestive tract? Does drug administration affect the digestive rate? what drugs? how? Does ingestion of alcoholic beverages cause any appreciable change in the same subject?

More questions and problems for research with the application of "microskatology" (the name I have given this particular branch of pharmacognosy) other than to forensic science, comes to mind, especially when considering pathological conditions. The color, consistancy of and presence of blood or pus in stools have long been used in the diagnosis of patho-

logical conditions. The use of the microscope might uncover clues to some conditions earlier than is now possible and early enough in some instances to start effective treatment. Do certain conditions cause changes in the vegetable structures, in the rate of passage through the digestive tract? in reaction to any particular reagents? Could some reagent have different effects on vegetable tissue under pathological conditions which would not occur in a normal environment?

These are just a few suggestions as to where the young pharmacognosist might find new fields to conquer. With some imagination and a lot of hard work, he might make a contribution to science of the first magnitude.

DISCUSSION

VanderWyk: How can you be positive of the identity of each of the food items you have mentioned?

Carpenter: The material was compared with authentic samples. I have gathered and preserved samples of a great number of foods, spices and coloring materials that are used by man. I will continue adding less common items as I come across them which will probably number well over 300 samples.

Youngken Jr.: Is there any apparent change in the stone cells of pear during digestion?

Carpenter: There is no apparent change either in morphology or reaction to common reagents, e.g., phloroglucinol.

(Several interested people looked over original slides in the laboratory and asked a number of pertinent questions following this examination.)

OBTAINING FUNDS FOR RESEARCH IN PHARMACOGNOSY

Edward P. Offutt

I want to express my thanks to your committee for giving me a second chance to bring a message to the Pharmacy schools. I regretted that last summer previous commitments kept me from meeting with the Pharmacologists. Really what I have to say is not specifically aimed at Pharmacognosy, you see, but is a general presentation on certain problems related to securing financial aid in support of research and teaching efforts.

My remarks today should not be considered to be related directly to my present position with the Smith Kline & French Foundation, though its courtesy makes it possible for me to be here. Rather, what I shall say stems from early academic concern with the support of medical research and education and later from service with the National Institutes of Health Grants Program and finally, in small measure, from my present post. Also, in this discussion, I shall draw from my contacts and experiences with other fund-granting agency personnel wherever possible.

For an audience such as this it seems appropriate to write a prescription for Dr. Offutt's treatment. The modest dose which I shall ask you to take with some frequency in the next half-hour I shall refer to as my "A-P-C" capsule.

The initial "A" suggests that first, one who seeks support should "Ascertain". By this I mean you should know from having made an inquiry whether a given potential source of money is active in dispensing its funds for the purposes which interest you. While it seems almost painfully evident that not every person is interested in what another is doing (and in this respect fund-granting agencies are like people), many individuals or organizations make applications for financial support in a completely haphazard fashion without any real hope of success. From experience I know that this can be damaging to morale, both personal and institutional. Also, it is a most inefficient use of your time and energy.

How best to "Ascertain" you ask? Personally, I believe a direct letter of inquiry to a given granting agency is desirable. A personally prepared letter to an organization asking for a statement of the areas of its interest will

usually bring a reply from someone concerned with allocation of funds. If you wish to direct it to one person, try the "Research Director" or "Director of Public Relations". Often the reply will provide rather precise suggestions for the method to be followed in making the specific approach. If the request is properly phrased it will rarely provoke a frank turndown until the question has been explored further. From the reply you may decide that there is no reason to apply to this agency for support if their interest does not extend to your problem.

Having "Ascertained" that there may be interest in your project, what next? "Propose"! The proposal you present should be as realistic as you can define it, in the interest of comparative and objective evaluation. I find few committee members reviewing grant requests who are attracted to the abstract or general; most are taken by the specific. Whether or not you and I agree this is desirable when support of basic research is at stake, it is well to recognize the fact when making your proposition. However, most grantors do not require precise details in the introductory phases of consideration. Thus, a concise, clear statement of your plan and requirements usually makes the most favorable impression.

I feel it is far better to have the preparation of this statement made by the proponent himself, rather than by some professional member of the development staff. The former usually presents a more accurate picture and in appropriate terms with proper emphasis on each portion. Believe me, though, if there is an officer in your institution involved with helping to prepare requests and required to approve their presentations to fund-granting agencies, this person should not be circumvented. To do so usually alienates the local situation and often complicates the connections away from home. The proposal should be constructed with care to assure that the requirements of the granting organization have been met.

I am ready for the next portion of my mnemonic, "C". This is "Consultation" and I would particularly emphasize it. Doesn't it make sense to have the best possible understanding between the main parties involved - the donor and the recipient? I feel it does and most individuals I know at the operating levels of my adopted profession agree. The best way I know for this to occur is to consult freely, one with the other. I grant you that our experience with evaluation committees and Trustees soon reveals what factors are most necessary to decision making and that in our urge to get decisions made we

may seem to emphasize only a small number of details. For my part, also, I feel the investigator should be spared as much unnecessary preparation as we can save him. Often the duties of my counterparts include preliminary screening of material submitted. This is another reason for effective "Consultation". You should use the opportunity to consult to aid you both at the time you seek initial help and for possible applications in the future.

You may wish some suggestions in preparation for your part in the "Consultation". Generally you will be thoroughly familiar with the subject matter of your proposition. Often, however, certain ancillary matters will require information you may not have at your finger tips. Lately a matter of greater concern to foundations, government, industry and to academic institutions is the position taken by each on patents which may conceivably result from findings made under grant support. Do you know how you and your institution stand on this matter? There is striking variation among institutions.

Another touchy subject is "overhead charges" or "indirect cost allowances". More and more academic administrators are feeling that research studies must pay at least a portion, if not all, of their way. Philosophically, the business manager is not at all opposed to a teacher doing research which utilizes an increasing extent of his time. But there are often significant costs related to a research program and it is not fair, the administrators feel, to require such research costs to be carried by generally meager institutional funds, particularly those previously allotted to further the teaching function. Many agencies supplying funds have strict regulations concerning overhead or indirect costs and the applicant for funds should understand the conditions of his own institution and the grantor in this matter. Particularly he should be certain an item for this expense is included in his budget if the administrators will require payment of indirect costs. Failure to do so will usually penalize the worker by taking away funds which he had planned to have for research.

As a generality under "Consultation", I would say that any question, which is unsettled in your mind, should be answered. I grant there is a practical limit to the number of inquiries you may want to make or the number of replies you may receive, but generally a complete mutual understanding is desirable.

It is now time to take our second dose. Before you take the next "capsule" I issue fair warning - I am substituting; a doctor's prerogative. I next propose new ingredients, though the capsule is still an "A-P-C".

This time "A" stands for "Ask", though this seems too simple. The fact remains that many people desirous and worthy of support do not ask; maybe I should say will not ask. Actually, nearly all sources of funds these days have a much greater demand for dollars than they can supply. Very few can afford to seek places to put their grants while still accepting voluntary requests for funds. It is therefore necessary to "Ask" and one should no longer feel that it is undignified to request support. The pattern in this regard is rapidly changing, where it has not already changed. No longer does an academic institution expect to support fully its investigator's research program; often it does not even support it in part. Today, only the technique of asking remains individualized and even now many applicants expect to "slant" their proposals to assure support.

Further, when you "Ask", specify a given sum and be sure it includes any routine charges required by your institution. Budgeting by fund-granting agencies is usually such a problem that requests for specified amounts become almost a "sine qua non" in their operations. Few among them have sufficiently fluid funds to adjust upward when additional needs suddenly appear.

When you"Ask" I suggest that you apply one other rule. Be realistic. State the real needs in your proposal even if you do not ask that all be met or do not expect that all will be. Too often I find applicants ask for far more than is needed for the proposed plan in the belief that if the reviewers recommend an award of less than the amount requested, an ample sum will still be available. A great number of times I have seen this technique fail. Reviewers will state: "This request is unreasonable"; "Maybe this man doesn't know what he wants to do"; "Get him to revise his estimates in line with his proposal". You may ask "Who are these reviewers?" I have to say that most often these are highly trained and respected individuals who truly do know the costs of performing research. At the other extreme, I would say that whenever an agency can save a significant number of dollars it is able to pay another grantee. In fairness to the next applicant, therefore, we usually strive to see that our funds extend as far as possible.

Having decided you are going to "Ask", you may then expect to "Present" your request. This presentation really represents the formalization of the proposal you have conceived earlier, including all of the refinements born of "consultation" and "ascertaining". Once again I reiterate, you should have reviewed your presentation to assure conformance with any regulations of the granting agency. Another thing, in relation to your presentation, you will want to check on is timing. Few agencies are sufficiently streamlined in their operations so that immediate service can be given. Often the larger the program the slower the "wheels of progress". You will want to allow time for the "mill to grind" and to prevent any need for regrinding by your failure to supply all the needed information. Indeed, many agencies will not consider an incomplete request.

Having "Asked" by way of a "Presentation", an applicant should recognize that in nearly every instance he is a competitor. This accounts for the second "C" which stands for "Compete". I can say that all programs of support of which I have knowledge are competitive ones and that in many instances the competition is rigorous. This is true because, in general, private sources of funds are not as large as Federal. In considering competition you probably do not need to be reminded that the Pharmacy School teacher and investigator has usually not been as aggressive as his confreres in Medical and Dental Schools. But I feel he should be; he needs to be in order not to be outdone. And surely there are many among you who are worthy and would be successful in competition if only you would seek out your appropriate event and compete strenuously in your specialty.

Before leaving this "C" I want to emphasize one other facet of "Competition". Even a champion is not always the winner. In general, competition improves performance. It is my observation that failure to procure a requested grant need not deter a man from continuing in competition. Another application may produce an award. In one large academic faculty the development officers responsible for the University's grants program indicate that their acceptance rate has been about 1 grant paid out of 4 applied for. But they are improving; it used to be 1 out of 5. With increasing amounts of money becoming available more awards will be made. We need to find more researchers rather than use the additional sums to grant larger awards. The supply of research workers today is not sufficiently large to fill all the present openings. The number of workers needs to increase to match the money available. So I say, do not give up easily. Compete

and compete again, if you fail to gain support at once. There is money available to do the studies you wish to do. The problem is only to discover the source and tap it.

I hope at this stage that none among you have decided that the treatment I recommend is worse than the disease. The third capsule is ready and will be the easiest to take, I predict.

I would fail you today if I did not pointedly indicate some sources of support. On Exhibit A I list addresses of some "Actualities". These are known industrial supporters of research in Pharmacy Schools including programs in Pharmacognosy. This list is not long but it represents a starter and was compiled from acknowledgements made in the public scientific press. In other words, these sources have been pleased to have (or may have insisted upon having) credit given to them in the footnotes of published papers. I am sure the list is not exhaustive. If any among you know of other industrial sources which have received public credit for support to research carried on in Pharmacy Schools I would be pleased to add these donors to my list. I mean to play no favorites and I would like to see the list extended.

Other "Actualities" can be seen from the second sheet I make available (Exhibit B). This shows that the National Institutes of Health Research Grants Program has extended into Pharmacy Schools, also. With greatly increased appropriations by Congress to the NIH, support from this agency will undoubtedly increase. The address from which to request information is: National Institutes of Health, Division of Research Grants, Bethesda 14, Md. Because this program is so large you will be unlikely to receive a personal reply. They will send descriptive literature.

From the short extract out of Secretary Costello's report, appended to the bottom of Exhibit B, you will note that less than $1,000,000 was contributed to Pharmacy Schools in 1958. Broken down, this amount represents only a little over $10,000 per school, not very much as grants go in the Federal programs. To me though, it is reassuring that support from government, from industry, and from foundations is roughly of the same magnitude. I am hopeful the situation may remain this way. Also, it is evident that Schools of Pharmacy are conscious of their stake in research. Grants from institution funds are nearly equal in number and in sum donated to support these projects. I am disappointed only by the fact that the total

number of grants figures out to barely 3 per school; that only 1 or 2 outside agencies may be supporting studies in a given school. This situation needs to be improved.

Before I leave the "Actualities" I'll mention Foundations. In general, each operates independently and according to its individual policy. This is why I have advised consultation and why I have preferred not to offer a list to you. I can speak with certainty only of my own affiliation. When I see only $135,000 ascribed to Foundations by Dr. Costello and realize that our small contribution last year into Pharmacy School programs accounted for more than 1/3 of this total, I wonder whether many other foundations are even active in supporting research in Pharmacy Schools. Apparently you and others in your profession have still another educational function to perform; a sales job to do. I believe that your manpower and facilities represent a resource not utilized to its full potential. If you make this point successfully, I am certain you will receive more support.

The "P" of this capsule signifies "Possibilities". As an association of the P.M.A. has passed a resolution and announced publicly its belief that basic or fundamental research should be fostered in the academic atmosphere of the University and its associated schools. To me this implies an obligation to support some of the work. Accordingly, member concerns of the P.M.A. which are not listed on my sheet should be considered as fair game when you are out hunting for support and may be worth a shot.

Other reasonable "Possibilities" among the Federal agencies include the Atomic Energy Commission, particularly for proposals involving radioisotope studies or training, and the National Science Foundation, for fundamental research. In certain special instances the Office of Naval Research, the Army, and the Department of Agriculture may have interest in and be potential supporters of your work. I consider the American Cancer Society, The American Heart Association and the National Foundation possibilities among the national voluntary agencies. All of these organizations have funds to expend for research.

My final "C" stands for "Conclusions". These are: Funds are available for research in Pharmacognosy. To obtain such funds it is necessary to specifically "Ask" for them, usually by means of a precise "Presentation" after "Ascertaining" which are appropriate sources and "Proposing" to and

"Consulting" with them. In most instances, even after this is done, a competitive process is required to select eventual grantees because there are usually more funds sought from a given source than are presently available. Success in "Competition" is rewarding and stimulates constructive activity in your chosen field. Historically, increased competition has begotten increased support.

KNOWN SUPPORTERS OF PROJECTS WITHIN PHARMACY SCHOOLS

American Chicle Co.,30-30 Thompson Ave.,Long Island City 1,N.Y.
Ames Co., Inc. 819 McNaughton Ave., Elkhart, Ind.
Atlas Powder Co.,Concord Pike & New Murphy Rd.,Wilmington 99.Del.
Burroughs Wellcome & Co., Inc.,1 Scarsdale Rd.,Tuckahoe 7, N.Y.
Ciba Pharm. Products, Inc.,556 Morris Ave.,Summit, N.J.
Colgate-Palmolive, 300 Park Ave., New York 22, N.Y.
Drug Specialties, Inc., Winston-Salem, N.C.
Fesler Co., Stamford, Conn.
Flint Eaton & Co., 300 E. Main St., Decatur 60, Ill.
Givauden-Delawana, Inc., 321 W. 44th St., New York 36, N.Y.
B.F. Goodrich Chemical Co.,3135 Euclid Ave.,Cleveland 15, Ohio
Heyden Newport Chem. Corp.,342 Madison Ave.,New York 17, N.Y.
Hoffmann-LaRoche, Inc., Kingsland Road, Nutley 10, N.J.
C.B. Kendall Co., Indianapolis, Ind.
Knoll Pharm. Co., 377 Crane St., Orange, N.J.
Lakeside Laboratories, Inc.,1707 E. North Ave.,Milwaukee, Wis.
Eli Lilly & Co.,740 S. Alabama St., Indpls. 6, Ind.
Miles Laboratories, Inc.,1127 Myrtle St.,Elkhart, Ind.
The National Drug Co.,4665-85 Stenton Ave.,Phila. 44, Pa.
Parke, Davis & Co., Jos. Campau Ave. at the River, Detroit 32,Mich.
Chas. Pfizer & Co., Inc.,11 Bartlett St.,Brooklyn 6, N.Y.
Pitman-Moore Co.,Div. of Allied Labs, Inc.,P.O.Box 1656,Indpls.6,
B.C. Remedy Co., Durham, N.C.
Sandoz Pharm.,Div. of Sandoz, Inc.,E. Hanover Labs,Rt.10, Box 11,
Hanover, N.J.
Smith Kline & French Labs.,1500Spring Garden St.,Phila. 1, Pa.
Smith Miller & Patch, Inc.,902 Broadway,New York 10, N.Y.
The Upjohn Co.,301 Henrietta St.,Kalamazoo, Mich.
Wallace Laboratories, 2 Park Ave., New York 16, N.Y.
Harry K. Wampole & Co., Inc., Stamford, Conn.
White Laboratories, Inc., Kenilworth, N.J.
Wyeth Laboratories, Radnor, Pa.

NUMBER of RESEARCH GRANTS AWARDED by PHS to SCHOOLS of PHARMACY

(From: Division of Research Grants, National Institutes of Health, Bethesda 14, Md.)
Fiscal Years 1951 - 1958

	1951	1952	1953	1954	1955	1956	1957	1958
University of Arkansas	-	-	-	-	-	-	-	1
University of California (S.F.)	3	3	4	2	1	1	2	2
Howard University (D.C.)	-	-	-	-	-	-	1	-
Drake University	-	1	-	1	-	-	-	-
University of Kansas	-	-	-	-	1	1	1	-
University of Maryland	-	-	-	-	-	-	-	1
Massachusetts College of Pharmacy	-	-	-	-	-	-	-	1
University of Michigan	-	-	-	-	-	-	-	1
University of Mississippi	-	-	-	1	1	1	2	1
St. Louis Coll. of Pharm. & Allied Sciences	-	1	1	1	-	-	-	-
University of North Carolina	-	-	1	1	1	-	-	-
North Dakota Agriculture College	-	1	-	-	-	-	-	1
Oregon State College	-	-	-	-	-	-	1	-
University of Rhode Island	-	-	-	-	-	-	-	1
South Dakota State College	-	-	-	-	-	-	-	1
University of Tennessee	-	-	-	-	-	-	1	-
Medical College of Virginia	-	-	-	-	-	-	-	2
University of Wisconsin	-	1	1	1	1	-	3	7
University of Wyoming	-	-	-	-	-	1	2	2
TOTALS: Grants - 67	3	7	7	7	5	4	13	21
Schools - 19	1	5	4	6	5	4	8	12

From: "Progress in Education," P. H. Costello, Secretary, American Council on Pharmaceutical Education, J.A.Ph.A., Practical Pharmacy Edition, Vol. 20, #6, June 1959

Total contributed to Colleges of Pharmacy, 1958: $830,264: (112 grants within institutions
(130 Grants from outside : ($135,000 + from Foundations
(200,000 + from Industry
(170,000 + from Federal Government

DISCUSSION

Youngken, Jr.: Is the list of donors or supporters of research complete for grants to the Colleges of Pharmacy?

Offutt: These are mainly from footnotes of published articles. Some of the companies are not happy to have their support bandied about among the fraternities.

Parks: You spoke of the American Drug Manufacturers' Association's recommendations for the support of research. There is no mention of Pharmacy in that recommendation.

Offutt: There is no mention of schools of Pharmacy either in the blanket recommendations by divisions of the Federal Government. They specifically mention schools of Medicine, Dentistry, Public Health, Nursing, and they omit Pharmacy too--this is no reason you should feel that you are ruled out. As far as I'm concerned you should be considered just as effective in the total picture as the schools of Medicine. I think they do mean to consider the Pharmacy Schools but haven't gotten around to it as yet.

Beal: In my applications in which I've been successful in receiving grants, I think the department of Pharmacognosy has been most successful in getting grants thus far.

Offutt: This may be an interesting device--but we do look pretty carefully into all phases of the applications.

Lord: In looking over this list of companies and their addresses, I wonder about locations. Is Smith Kline French Foundation at the same address as the company?

Offutt: I have ruled out the foundations. Our foundation does not handle anything that is of particular interest to the laboratory. If an item is such that it can be considered a business deduction of the company the foundation is not legally able to touch it. The company may feel that you want to do something that they would not approve in their scheduled program--but since it happens in the field of interest to the company they may not be able to take part in the support of the work. This is unfortunate but it operates this way with a number of companies.

Youngken, Jr.: I wonder if you would be willing to add another company to your list. The S. B. Penick Company has helped a number of us with information as well as some funds in the carrying on of our research program.

Beal: What is meant by a year listed on your sheet?

Offutt: It is the fiscal year of the organization.

THE USE OF RADIOACTIVE ISOTOPES IN PHARMACOGNOSY

Ara G. Paul

In the preface to his book "Radioisotopes in Biology and Agriculture", C. L. Comar (1) states "Radioisotope techniques, to the naive, may represent the panacea for investigational difficulties--the royal road to successful experimentation; to the cynic they may appear as gadgetry, a fad that creates more problems than it solves. As always, the truth lies somewhere between the extremes. The really important contributions of these procedures in the biological field will be realized only insofar as they are utilized by investigators who are well grounded and have been working in the field of application. This is not to belittle the physical scientist, whose tremendous contribution is acclaimed by all. Nevertheless it is the biologist who recognizes the important problems in his own field, is familiar with the experimental material, and must be counted upon to make the interpretations."

What Comar has said of biology in general, holds true for pharmacognosy as well. Radioisotope techniques are merely another research tool. One must learn how to properly manipulate the tool but equally important, one must recognize where it may be applied most successfully.

In 1948 Christian (2) suggested that radioisctopes might effectively be used in pharmacognosy in studies of the mechanisms of biosynthesis of medicinal products and in the production of isotope-labeled medicinals of natural origin. Some five reports in these areas of investigation have been published by pharmacognosists since that date. Hence my discussion today will restrict itself to a reiteration of Christian's suggestions, with one or two additions, rather than a review of what has been accomplished thus far.

Studies of the Mechanisms of Biosynthesis of Medicinal Products

Of purely academic interest are studies which concern themselves with how plants produce compounds which we as pharmacognosists are inclined to be interested in. Prior to the availability of carbon-14, the techniques employed in such investigations required that a suspect precursor cause a quantitative increase in the amount of the compound under investigation. The pitfalls of such a technique are aptly described by James (3) and are familiar to most of us.

With the availability of carbon-14, the area of biosynthetic experimentation underwent a rapid change. Rather than depending upon quantitative increases as proof of the role played by a precursor, the investigator now had a tool which required only that qualitative conversion be demonstrated. A recent review by Marion (4) describes, in part, the successful applications of radioactive isotopes toward the elucidation of the pathways of biosynthesis of several alkaloids. The techniques used are equally applicable to the study of other plant products.

Three general methods may be used in such studies; whole plant feedings, tissue cultures and enzymatic extracts.

In experiments using the entire plant, one must first determine the age at which biosynthesis of the particular constituent under investigation is actively carried on. The plants are then grown by the usual technique, and at the proper time transferred to a nutrient solution containing the radioactive suspect precursor. After a suitable growing period, the plants are harvested, the constituent is extracted, purified and assayed for radioactivity. When dealing with relatively large quantities of material, standard procedures of isolation may be used followed by quantitative assay for radioactivity using an end-window counter, a windowless flow counter or a liquid scintillation counter. When only small quantities of material are available, it is more convenient to use paper chromatography for the resolution of the constituent followed by autoradiography to detect the presence of radioactivity.

Use of the whole intact plant in biosynthesis studies offers several advantages. The plant can be said to be functioning "normally" and hence any data, whether positive or negative, can be considered valid. Also, relatively large quantities of material can be handled and consequently the constituent under investigation can usually be more easily isolated. One apparent disadvantage of the technique is the result of the septic conditions under which the plant is grown. Microbial growth and utilization of the test compound during the term of the experiment can conceivably give rise to erroneous interpretation of data. Various germicidal detergents which reportedly do not adversely effect the plant, are commonly used in the nutrient solution to inhibit microorganisms.

Tissue culture techniques as a means of studying biosynthetic pathways offer the advantage that aseptic conditions

prevail throughout the growing period. However, the relatively small quantities of tissue which can conveniently be grown are a decided drawback.

The use of tissue homogenates and enzyme extracts have not as yet been successfully applied to studies of the pathways of biosynthesis of medicinal products. In most respects this method would be ideal; the time required of the experiment would be a matter of hours as opposed to the weeks involved in the two other technics. One need not be concerned with the septic conditions under which the experiment is carried out; the short time and the use of growth inhibitors eliminate chances of microbial growth giving rise to erroneous results, Because of the nature of the technic, however, only positive data may be considered valid.

Through the use of radioisotopes the investigator can not only demonstrate the conversion of one compound to another but, further, by specifically labeling various positions of a suspect precursor with an isotope, he can demonstrate which portion of it contributes to a particular portion of the compound under investigation. For example, through the use of methionine labeled only in the methyl group with carbon-14, Brown and Byerrum (5) were able to demonstrate that this carbon atom could give rise to the methyl carbon of nicotine. To prove that the methyl group was transferred as a unit, rather than oxidized to the state of formaldehyde and later reduced, methionine doubly labeled in the methyl group with carbon-14 and deuterium was administered to the intact tobacco plant (6). The results established that the mechanism was transmethylation.

Though the use of radioactive isotopes as tools for elucidating pathways of biosynthesis may at first glance appear to be ideal, there are certain drawbacks which must be considered. The radiochemical purity of the isotope-labeled compound is extremely important and should be determined on any test compound used in such investigations. This is especially true of studies which rely solely upon paper chromatography followed by autoradiography to detect radioactivity in the final product. Organic compounds labeled with carbon-14 are expensive, often prohibitive and while tritiated compounds are considerably cheaper, often they will not serve the purpose. Laboratory facilities and equipment required for these investigations add to the financial burden.

Production of Isotope-labeled Medicinals of Natural Origin

The incorporation of carbon-14 into medicinals provides a sensitive method of detecting these compounds in quantities which cannot accurately be detected by the other chemical and biological technics.

Compounds so labeled can effectively be used by the pharmacologist to study the distribution and fate of medicinals in animals. Further they may be used by the pharmacognocist in studies of the biosynthesis of these compounds. When chemical synthesis is impractical or impossible, biosynthesis must be relied upon. To date there are reports of only ten medicinal compounds produced in this fashion.

At the Geneva Conference (7) Scully et. al. described the construction and design of plant growth chambers utilized for the propagation of plants in $C^{14}O_2$. In addition there is a relatively complete discussion of such factors as CO_2 concentration, C^{14} activity, temperature, humidity, daylength, light intensity, etc. Slide 1 shows a schematic diagram of the Argonne-Type Plant Growth Chamber.

Plants may be grown under more modest conditions as well. Slide 2 shows a group of plants sealed in bell jars.

Problems are encountered in growing plants in an atmosphere of $C^{14}O_2$. Little work has been done on the radiosensitivity of plants. The incorporation of C^{14} into the plant provides a continuous source of beta radiation. The level of activity maintained in the chamber is governed by the level of activity one desires in the final product. However in arbitrarily choosing a level of activity one must face the risk that undesirable effects may result in an abnormal plant and perhaps reduce the yield of the material one desires. With little data available, there is no choice but to experiment on a modest scale with various levels of activity prior to undertaking a large scale biosynthesis. It may also be possible that prolonged growth of the plants under $C^{14}O_2$ could be avoided by growing the plants at very high levels of activity just prior to and during the period when active biosynthesis of the constituent is taking place. If current photosynthate is utilized in the production of the constituent, the level of activity should be relatively high.

The Production of Desirable Mutants in Medicinal Plants.

A third area of investigation which has been ignored by most pharmacognocists concerns itself with the production of genetic mutants of medicinal plants which conceivably yield greater quantities of a given constituent. Traditionally we have relied upon spontaneous mutation and segregation following hybridization for our sources of genetic variability. Ionizing radiations speed up the supply of new mutations and though the greatest number of themare undesirable or deleterious, a few give rise to desirable characteristics. With the availability of nuclear reactors, one now has at his disposal various forms of radiation; beta particles, protons, fast and thermal neutrons, and multicurie gamma-radiation sources.

In the field of agriculture plant breeders have induced a wide variety of mutations in economically important plants; increased protein and oil content of cereals, fruits of better taste and marketing qualities, etc. There is no reason to believe that the production of desirable mutants in medicinal plants is not possible.

The use of radioisotopes in pharmacognosy by pharmacognocists has been sorely lacking. Many problems which conceivably could be clarified through the proper use of this research tool remain unanswered. I sincerely hope that the next ten years will see us take advantage of the opportunities offered us by these "by products" of atomic energy.

Bibliography

1. Comar, C. L., "Radioisotopes in Biology and Agriculture", McGraw-Hill Book Co., Inc., New York, 1955.
2. Christian, J. E., J.A.Ph.A., Sci. Ed. 37, 250 (1948).
3. James, W. O. in "The Alkaloids", Vol. I, Manske, R. H. and Holmes, H. L., eds., Academic Press Inc., New York, 1950,p.56.
4. Marion. L., Bull. soc. chim France. 109-115 (1958).
5. Brown, S. A. and Byerrum, R. U., J.A.C.S. 74, 1523 (1952).
6. Dewey, L.J., Byerrum, R. U., and Ball, C. D., J.A.C.S. 76, 3997 (1954).
7. Scully, N.J., et al., in "International Conference on Peaceful Uses of Atomic Energy, Geneva," Vol. 12, United Nations, New York, 1955, pp. 377-385.

Supplementary Bibliography

Glasstone, S., "Sourcebook on Atomic Energy, 2nd ed.", D. Van Nostrand, Princeton, N.J., 1958

Kamen, M.D., "Isotopic Tracers in Biology, 3rd ed.", Academic Press Inc., New York, 1957.

Quinby, E. H., Feitelberg, S. and Silver, S. "Radioactive Isotopes in Clinical Practice", Lea & Febiger, Philadelphia, 1958.

Faires, R. A. and Parks, B. H., "Radioisotope Laboratory Techniques", Pitman Publishing Corp., New York, 1958.

Bugher, J. C., Coursaget, J., and Loutit, J. F., "Progress in Nuclear Energy", Series VI, Biological Sciences, Pergamon Press, New York, 1956.

DISCUSSION

Question: The laboratory at Oak Ridge sells irradiated seed--about a half ounce of any seed which has been exposed to Cobalt-60 radiation. Are you aware of this?

Paul: Much work has been done on plants that have been irradiated. These are used for propagation, agricultural treatments of various types. Cobalt-60 is the highest source of irradiation that one can achieve in a short period of time. Prior to this we were limited to X-ray machines. In addition to Cobalt-60, plant irradiation by neutrons, protons, and beta particles in various intensities have been used to bring about genetic changes.

Question: Are you acquainted with any reviews on this general subject?

Paul: There are several reviews that are good for the techniques of radioactive isotopes. A book by J. C. Bugher, J. Coursaget and J. F. Loutit, "Progress in Nuclear Energy, vol. VI"

Sparrow recently reviewed botanical aspects in Science.

Cole: What sort of shielding problems do you have in radioactive CO_2 administration?

Paul: None whatever, C^{14} has a weak beta emitter radiation.

The only problems involved are getting rid of the CO_2 after it has been used in the chamber. Monitors should be low.

Farnsworth: Is it possible to label chemical constituents in the plant by another method besides exposing them to radioactive CO_2?

Paul: Yes. Introduce a radioactive precursor into the plant and allow this to be taken up by the plant.

Farnsworth: In a situation like this, could you label, e.g., Digitoxin by taking some harvested leaves and exposing them to radioactive material, not a living plant?

Paul: Exposure of the leaf to radioactive CO_2 or to radioactive precursors would accomplish this.

APPLICATIONS OF INSTRUMENTATION TO PHARMACOGNOSY

Egil Ramstad and Adelbert Knevel

Simple, accurate and speedy methods are no less vital for success in pharmacognostic research than in other sciences. Pharmacognosy, being an applied science, has no methods unique to itself, and its development is intimately linked to the progress in other branches of science.

The improvements in microscopic techniques and taxonomic endeavors of the last century led to an intense activity in these areas of pharmacognosy also. The chemical successes of the latter half of the last century and of this one are now, in a sense, mirrored in the phytochemical activities of many pharmacognosists today. Not only have advances in methodology put problems of structural chemistry into the field of pharmacognosy, but the explosive development and expansion of biochemistry have induced pharmacognosy to bloom. This is to be expected, for the most basic concern of pharmacognosy centers about the chemical and biochemical problems of therapeutic components of the cell. Our interest in these elements leads us not only to a desire for understanding of the normal goings-on in the cell, but even further, to a concern and study of the relationships between normal cell metabolism and the production of therapeutically active components. These compounds must often be locked upon as abnormal products of cell metabolism. This area is a unique and characteristic field of pharmacognosy as a science, and so is the study of the changes that hereditary and environmental factors impose upon the activities of the cells of the drug-producing organisms. Without such knowledge we shall have a difficult time in providing the best conditions for the drug-furnishing organism to produce the best possible quality and to minimize deterioration of the drug.

Investigations into the complexities of cellular occurrences require the use of effective methods of separating molecules and, as we have learned, such methods are abundantly available. In addition, we generally are in need of quantitative information, often to be obtained from minute samples. Sometimes we want quantitative information without first having to isolate the compound in question. In other cases, we want information about structures of the compounds, as an aid in their identification. It is primarily in these two areas that instrumentation gives us the invaluable help. Fortunately,

most instrumental methods require small samples and are non-destructive to the compounds under investigation. This is truly important when only small quantities are available and the sample must be recovered for additional analyses.

The term "instrumentation" has several meanings, but we understand it in this context to mean the use of instruments for analytical purposes, to measure physico-chemical properties. Each area of science and technology has designed numerable instruments for specific purposes. Although we are fully aware that many instruments occasionally are used by pharmacognosists for special purposes (Warburg respirometer, electron microscope, ultra-centrifuge, etc.), we would like to restrict this talk to polarography and spectrometry (ultraviolet, fluorescence, visible, infrared and nuclear magnetic spectrometry), as we judge these fields to be of most interest to seminarians.

Polarographic analysis

Polarographic analysis can be applied to many plant products. In this method a solution of the material being analyzed is put in contact with a dropping mercury electrode of increasing voltage where it is usually reduced or oxidized. The electrical potential between beginning value and maximum reaction is measured on the automatically recorded polarogram. The half-wave potential constitutes a value characteristic of the material and can serve to identify the compound. Since the height of the wave of current flowing through the solution is proportional to the concentration of the material, it may be used to determine the concentration. The method is reasonably sensitive as most substances may be determined in concentrations as low as 10^{-6}M. In fact, this is its main application since, for qualitative work, only one parameter would be available. For the same reason the method is generally most suitable for the measurement of rather pure compounds, but in certain instances can be used with crude mixtures. For instance, aloin can be determined accurately in aloe, carvone in caraway oil, ascaridole in chenopodium oil, fructose in fruits or honey, α-ketoglutaric acid in fermentation medium, and many others. The method may be very valuable in distinguishing among related compounds. For example, polarographic analysis of many cardiac glycosides containing a double bond in the α,β positions of the lactone ring shows half-wave potentials in the vicinity of -2.0 volts. On the other hand, saturated lactone rings are not reduced polarographically. Thus, if analytical data suggests the presence of a lactone

ring in the characterization of an unknown compound, polarographic data would give further evidence for the presence or absence of α and β unsaturation (1). Brezina and Zuman have recently published a comprehensive book on the method of polarography in medicine, biochemistry and pharmacy in which is provided polarographic data for many plant constituents (2).

Spectrometric analysis

In recent years, no type of instruments has contributed more to the advancement of chemistry of natural drug products than the several types of instruments measuring the interaction of chemical compounds and radiant energy. Instruments are now available for such measurements for almost any part of the wave spectrum.

As we know, the shaking and twitching of the molecule are due in part to vibrations set up by the spinning of the end-groups in the molecule and to vibrations caused by stretching, compressing or bending of bonds between the atoms. Additional vibrations in the molecule due to the overall effect of the many individual twitchings are many and become rather specific for each chemical compound, but are difficult to interpret when recorded.

Whatever their cause, the vibrations are characteristic for the chemical structure causing them, and under certain conditions, interfere with electromagnetic radiation of matching wavelength causing quenching or absorption of the wavelength in question. Thus, by plotting the specific wavelength versus the radiation absorbed, we obtain information about the structural nature of the compound under investigation. A determination of the degree of absorption (absorbancy) gives us a measure of the quantity of the compound. The more complex a compound, the higher are the numbers of different modes of vibrations and the more complex its absorption spectrum. Also, the nature of the neighboring group displaces the frequency of the vibration slightly. Thus, the extent of the displacement gives additional information. It is probably safe to state that two different compounds will not show the same absorption throughout any wide length of the spectrum, so that the spectrum becomes a very characteristic feature of any organic compound.

The regions most exploited extend from 2.0 to 15.0 microns in infrared spectroscopy, 0.4 to 0.7 micron, which constitutes the entire visible region, and 0.2 to 0.4 micron for ultraviolet

spectroscopy. The radio-frequency region is used for nuclear magnetic resonance spectroscopy and the X-ray region for X-ray spectroscopy.

The versatility, reliability and convenience of most spectrometric methods make them truly choice methods in many cases. Instruments for use in the ultraviolet, the visible and the infrared regions of the spectrum are becoming more and more common in analytical laboratories, while use of radio-waves and x-rays has been restricted mostly to physical laboratories.

Absorption and partition chromatography, electrochromatography, ion-exchange resins and, in many cases, isotopes have facilitated phytochemical, structural and biochemical investigations to a point where the most complex problems can be attacked. Spectrometric methods, however, complement these methods in giving additional information. A few examples will illustrate such uses:

In the study of biosynthesis of erythromycin, and in the commercial production, large numbers of accurate determinations must be carried out. Two ways are open: the time-consuming and laborious microbiological method and the colorimetric method. Studies of the reaction products of erythromycin in the broth show that the alkaline hydrolytic products have a specific absorption maximum at 236 millimicrons and they obey Beer's law. It can be shown that other compounds of the medium do not interfere and that the results correspond excellently with those from the microbiological assays. The method saves endless hours of work and is economical in material (3).

Usually, the determinations are carried out only after solvent-solvent extraction, complexation, chromatography, or some other preparatory step. Actually, a similar approach is possible with many comparatively crude preparations and has been used, for instance, in the determination of alkaloids in opium (4), in belladonna (5), and theobromine in cocoa (6). In other cases, the measurements have been performed directly with the cultural medium or with the crude extracts. For example, production of clavine alkaloids by Claviceps has been followed by measuring the extent of absorption at 590 millimicrons after treating the cultural medium with p-dimethylaminobenzaldehyde, a reagent specific for indole nuclei, followed by exposure to ultraviolet radiation for the purpose of intensifying the color (7).

An advantage of ultraviolet spectrometry is that only a small quantity of sample is needed. Yet, in some types of work, such as in biosynthetic studies, we often have only trace quantities. In such cases, fluorometry has definite advantages over ultraviolet spectrometry, since it is 100 to 1000 times more sensitive than the latter. For instance, aesculin in quantities less than 0.1 microgram and quinine in concentrations as small as 0.02 microgram per milliliter can be determined accurately. In fact, high dilution is a necessity; otherwise self-quenching of the fluorescence will occur.

In spite of its sensitivity, fluorometry has generally been looked upon with suspicion, particularly because of the difficulty of producing activating light of sufficiently high intensity over a wide range of wavelengths. These problems have now been largely solved and fluorometry is picking up fast as an analytical method (8).

Fluorescent substances pick up radiant energy of various wavelengths and release the energy in the form of longer wavelengths. Naturally, some compounds may emit ultraviolet energy, invisible to the eye, but still are suitable for fluorometric analytical work. Determining the intensity of fluorescence at the various activating wavelengths furnishes the activation spectrum. In addition to the activation, the instruments also record the spectrum of the emitted light - the fluorescence spectrum. Thus, it becomes possible to make use of one or both of these spectra for identification and for quantitative measurements. In quantitative estimations one must, however, be on the lookout for possible presence of quenchers; for instance, phosphate esters will quench the fluorescent activity of quinine (9). In some cases it is possible to determine two fluorescent compounds simultaneously by making use of wavelengths far enough apart to excite only one but not the other compound of the mixture. It is not necessary to choose the highest peak. For instance, thiamine (as thiochrome) can be determined fluorometrically along with riboflavin (0.6 micrograms/ml.) without previous separation (10).

Both activation and fluorescence maxima have been published for many biologically important compounds (11). An interesting method for working with cardiac glycosides has been published by Bellet (12). Cardenolides with a hydroxy group in position 16, such as digitoxigenin and gitoxigenin form fluorescent di-anhydro derivatives with hot phosphoric acid and thus can be identified and quantitatively estimated by means of their fluorescent spectra.

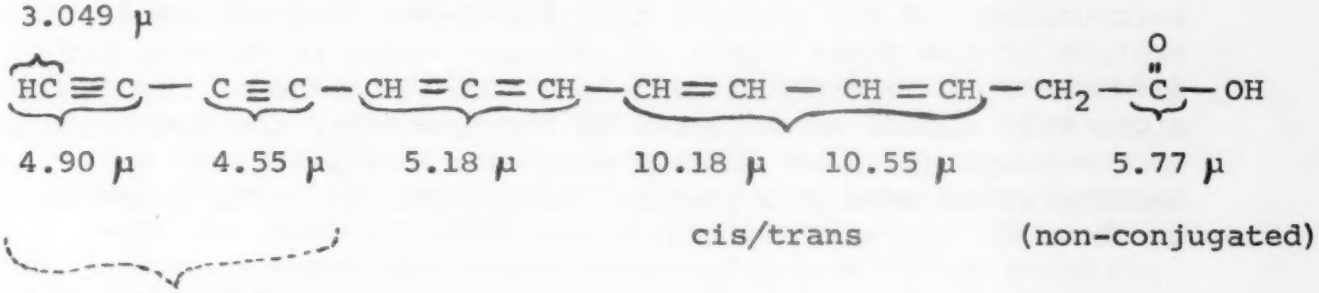
Absorption in the infrared portion of the spectrum (13) generally furnishes more information about the structure of a compound than other regions, except perhaps x-ray and electron diffraction, but the latter, so far, has been in the realm of pure physics. Infrared spectrometry permits the study of compounds in solution or in the solid form and is feasible down to quantities as small as 10 micrograms (micro attachment) although 2-4 mg. are usually used. Infrared spectrometry can be used for qualitative and also quantitative work, since the absorption generally follows Beer's law. A disadvantage of the method as a quantitative tool is the complexity of the absorption spectra so that great care is needed for selection of absorption peaks that are not given by solvents or by contaminants. It is also comparatively less sensitive than the U.V. and the fluorometric methods.

Application of infrared spectrometry to pharmacognosy falls into two groups: (1) identification and (2) structural studies.

Identification of compounds can be done by comparison of infrared spectra of the unknown and the authentic material or its recorded spectrum as reported in the literature or deposited at the American National Bureau of Standards, British National Depository and other places.

Molecular vibrations interacting with various wavelengths in the lower infrared region (2.6-7.4 microns) are caused by specific chemical groups (H-, CH_3, etc.), while the skeletal vibrations lay in the higher region (7.5-14 microns), the so-called "fingerprint" region. This latter region is most valuable in the specific identification of a compound by comparison of spectra since two different compounds have not been found that give exactly the same spectrum. The problem of identifying a new constituent of drugs is often complicated by the fact that, generally, it consists of one optical isomer while the synthetic compound used for comparison consists of the dl racemic mixture. However, optical isomers in solution give the same spectra so that an isolated compound can be directly compared with the synthetic compound. The advantage of this "fingerprint" identification becomes more evident when one recalls that different isomers commonly have different melting points. Naturally, an infrared spectrum is far superior to mixed melting points or chromatography, since so many more parameters must be satisfied.

For structural studies, the vibrations of specific functional groups of molecules have now been studied so thoroughly that we are well informed about their areas of absorption. Also, the small displacements that result from the neighboring groups have been studied. Today, therefore, one can read the presence of specific functional groups directly from the infrared spectrum. A good example of its usefulness for structural studies can be given from the work on the antibiotic mycomycin (14). ($C_{13}H_{10}O_2$)



Nuclear Magnetic Resonance

During the decade since Purcell and Bloch discovered the phenomenon of nuclear magnetic resonance, instrumentation in this field has developed rapidly, so that, today, NMR, as it is conveniently called, has already become an important analytical tool used to solve a variety of problems in chemistry. (15) To the pharmacognosist NMR probably is most valuable for structural studies of organic compounds.

The utility of NMR is based on the fact that the hydrogen nucleus, the proton, is charged and spinning and thus acts as a floating magnet with a fixed axis like a gyroscope. If the proton magnet is exposed to a strong outside magnetic field it is brought to wobble (precess) like a gyroscope, increasing in speed as the intensity of the magnetic field is increased. By placing another magnetic field at 90° angle to the first and making it rotate at exactly the speed of the wobbling proton, the proton is forced to tip over, a process that requires consumption of energy. This energy can be detected and measured and appears on a recorder or oscilloscope as a peak. The rotating magnetic field is controlled by radio waves from an oscillator. One can determine either the strength of the first magnetic field at constant wavelength (i.e., constant speed of rotating magnetic field) or one can

determine the radiofrequency needed to tip over the protons when the first magnetic field is kept constant.

The value of this principle to analytical chemistry resides in the fact that the magnetic fields created by protons of hydrogen atoms in different surroundings of other atoms are shielded to different degrees due to differences caused by surrounding electrons and other topographic conditions. Thus the exact strength of the primary magnetic field (or the required radiofrequency) tells the precise nature of the surroundings of the protons that tip over. For instance, the protons of the three types of hydrogen atoms in ethanol are differently shielded and hence the three protons of the methyl group will appear as one peak on the spectrum, the two protons of the ethyl group as another peak, and the proton on the hydroxy group as a third peak. An example of a NMR spectrum is shown.

REFERENCES

1. Shostenko, T. V. and I. J. Uralova, Zhur. Obshei. Khim., 21, 143 (1951)
2. Brezina, M. and P. Zuman, Polarography in Medicine, Biochemistry and Pharmacy, Intersc. Publ., N. Y., 1958
3. Tepe, J. B. and C. V. St. John, Anal. Chem., 27, 744, (1955)
4. Oyer, M. S. and A. J. McBay, J. Am. Pharm. Assoc., Sci. Ed., 44. 156 (1955)
5. Worrell, L. and R. E. Booth, ibid., 42, 361 (1953)
6. Hively, R. A. et al., Anal. Chem., 27, 100 (1955)
7. Tyler, V. E., J. Am. Pharm. Assoc., Sci. Ed., 47, 787 (1958)
8. Bartholomew, R. J., Rev. Pure and Appl. Chem., 8, 265 (1958)
9. Rorem, E. S., Nature 1959, 1739
10. Ohnesorge, W. E. and L. B. Rogers, Anal. Chem., 28, 1017 (1956)
11. Duggan, D. E. et al., Arch. Bioch. and Biophys., 68, 1 (1957)
12. Bellet, M., Ann. Pharm. Franç, 8, 471 (1950)
13. Cole, A. R. H., Fortschr. Chemie org. Naturst., 13, 1 (1956)
14. Celmer, W. D. and T. A. Solomons, J. Amer. Chem. Soc., 75, 1372 (1953)
15. Roberts, J.D., Nuclear Magnetic Resonance, McGraw-Hill Publ., N. Y., 1959

DISCUSSION

Schwarting: I have found that Physical chemists are very careful about explaining something outside of their particular area of interest and work. It is hard for them to evaluate a new compound, particularly a natural product. They are not free to evaluate an infra-red spectrograph. When will the point come when it will be possible to get a good interpretation of an infra-red spectrograph that has been made of an isolated compound?

Knevel: I firmly believe that the interpretation of a spectrum such as you suggest will not come. Those working on the identification of new compounds will use the infrared and ultraviolet techniques only to complement and supplement the standard good analytical procedures. When we take a compound and our spectrograph pictures to our physical chemists they ask what we think we have. They can verify the presence or absence of the compound in question and that's the best that can be done. When infrared spectra can be completely superimposed on each other you can be sure that the same compound is involved in both spectra.

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